CLINICAL ENDOCRINE AND METABOLIC STUDIES IN MEDICAL CONDITIONS CHARACTERISED BY HYPOXIA

A Thesis submitted

by

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GLOSSARY AND ABBREVIATIONS

GENERAL

BLUE BLOATERS	COAD with hypercapnia
CBF	Cerebral blood flow
CCHD	Cyanotic congenital heart disease
COAD	Chronic obstructive airways disease
COR PULMONALE	Right ventricular hypertrophy/failure secondary to hypoxic lung disease
^{51}Cr	Isotope of chromium
CRCF	Cerebral red cell flux (CBF x haematocrit)
CV	Closing volume
ECW	Extracellular water
EME	Early morning penile erection
FEF 75-85%	Forced expiratory flow rate between 75 to 85 per cent of vital capacity
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
H-P-T	Hypothalamo-pituitary-testicular
HYPERCAPNIA	Arterial carbon dioxide tension of high level
HYPOXIA	Arterial oxygen tension of low level
^{125}I	Isotope of iodine
ICK	Intracellular potassium
ICW	Intracellular water
LBM	Lean body mass, fat free mass
MMFR	Maximum mid-expiratory flow rate
MENARCHE	Onset of menstruation
NA	Not asked
ND	Not done
NORMOCAPNIA	Arterial carbon dioxide tension normal
NS	Not significant
OLIGOSPERMIA	Low sperm count

$PaCO_2$	Measure of arterial carbon dioxide tension
PaO_2	Measure of arterial oxygen tension
PEFR	Peak expiratory flow rate
PICKWICKIAN	Obstructive sleep apnoea syndrome
PINK PUFFER	COAD with normocapnia
$POTASSIUM^{40}$	Isotope of potassium
PV	Plasma volume
RCV	Red cell volume
REM	Rapid eye movement
RLD	Restrictive lung disease
RV	Residual volume
SHBG	Sex hormone binding globulin
SI	Sexual intercourse
TBK	Total body potassium
TBW	Total body water
TF	Single breath transfer factor (diffusing capacity)
TIBC	Total iron binding capacity
TLC	Total lung capacity
UD	Undetectable
133Xe	Isotope of xenon

HORMONES

ABBREVIATION	HORMONE	SOURCE
A/Dione	Androstenedione	Adrenal and testicular
ACTH	Adrenocorticotrophic hormone	Anterior pituitary
-	Aldosterone	Adrenal medulla
ADH	Antidiuretic hormone	Posterior pituitary

-	Cortisol	Adrenal cortex
DHA	Dehydroepiandrosterone	An adrenal androgen
DHAS	Dehydroepiandrosterone sulphate	An adrenal androgen
FSH	Follicle-stimulating hormone	Anterior pituitary
GnRH	Gonadotrophin releasing hormone	Hypothalamus
HGH	Human growth hormone	Anterior pituitary
17-KS	17-Ketosteroids	Metabolites of testosterone
LH	Luteinising hormone	Anterior pituitary
-	Oestradiol	Conversion from androgens
17-OHA	17-Hydroxyandrogens (testosterone)	Leydig cell-testes
17-OHCS	17-Hydroxycorticosteroids	Metabolites of cortisol
-	Prolactin	Anterior pituitary
-	Testosterone	Leydig cell-testes
TRH	Thyrotrophin releasing hormone	Hypothalamus
TSH	Thyroid-stimulating hormone	Anterior pituitary
T_3	Tri-iodothyronine	Thyroid
T_4	Thyroxine	Thyroid

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FIGURE 25 Sequential measurements of serum thyroxine, triiodothyronine, thyroid binding globulin and free thyroxine in a man with obstructive sleep apnoea (Pickwickian) syndrome during weight reduction diet

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CLINICAL ENDOCRINE AND METABOLIC STUDIES IN MEDICAL CONDITIONS CHARACTERISED BY HYPOXIA

SUMMARY

The thesis embraces fourteen related projects carried out along with various willing colleagues in several Scottish hospitals over nine years and most of the findings have been published (reprints enclosed).

In the first clinical and illustrated autopsy studies of Scottish patients with severe emphysema associated with alpha-1-antitrypsin deficiency, we found weight loss to be a frequent accompaniment of the panacinar emphysema. Though decreased calorie intake had been claimed to be a cause of weight loss in emphysema scrutiny of the evidence suggested other factors to be involved. My early research endeavoured to cast light on reasons other than genetic for such weight loss and for the contrast in body habitus between emphysematous 'pink puffers' and bronchitic 'blue bloaters'. The early results provided more questions than answers and set the stage for the further work described in the thesis.

In our pilot studies searching for metabolic abnormalities, low total body potassium values, believed to indicate lean tissue loss, were found in both 'pink puffers' and 'blue bloaters'. Though the latter group were considerably heavier they showed no difference in calorie intake or dietary absorption. Anabolic steroid studies showed major changes including low levels of serum testosterone especially in blue bloaters while the pink puffers in addition had high levels of the adrenal androgen dehydroepiandrosterone. We felt these endocrine patterns might to some extent be effecting physical

characteristics in the two groups.

A further study of similar patients confirmed a correlation between the level of hypoxia, but not of hypercapnia, and the degree of testosterone reduction and indeed eighty per cent of patients with a PaO_2 below 6.6kPa (50mmHg) had low serum testosterone levels. The association which to us strongly suggested a causal relationship had never previously been described.

Combined pituitary stress tests in these patients indicated suppression of the hypothalamo-pituitary-testicular axis while other aspects of hypothalamic and pituitary function were comparatively well preserved. Evidence was found that the hypothalamus rather than the pituitary was responsible for the deficient steroidogenesis.

Similar but not identical endocrine abnormalities were found in patients with hypoxic restrictive lung disease (pulmonary fibrosis) and here in some cases pituitary rather than hypothalamic suppression seemed responsible for the low testosterone levels. Individuals with cyanotic congenital heart disease, similarly hypoxic, had normal testosterone values perhaps because they have tolerance to hypoxia from birth. A parallel may be drawn between visitors at high altitudes who develop low testosterone production and high altitude natives who, though similarly hypoxic, retain normal levels.

As an appendix we have reported a case of obstructive sleep apnoea (Pickwickian) syndrome. Rapid weight gain following cessation of smoking was accompanied by onset of sexual impotence and bouts of somnolence. Frankly low serum testosterone levels were found but after weight reduction, which improved respiratory function and oxygenation, testosterone levels became normal and sexual potency returned. Although sexual impotence had been noted previously in this rare syndrome, the hormone changes had never been described.

A study of patients in acute phase cor pulmonale confirmed low levels of serum testosterone, luteinising hormone, follicle stimulating hormone and dehydroepiandrosterone. They had all risen on recovery three months later along with improvement in arterial oxygen tensions thus offering further evidence of hypoxic suppression of the hypothalamus and/or pituitary and also illustrating that such suppression is reversible.

Possible consequences of low testosterone production were investigated. Hypoxic respiratory patients were found to have diminished libido and evidence of organic sexual impotence which varied with disease severity, arterial oxygenation and testosterone values. This contrasted with normal sexual function in men with cyanotic congenital heart disease and comparable hypoxia.

In a study of ill patients during acute phase cor pulmonale and also later when considerably improved, low values of total body potassium fell further reflecting a continuing fall in lean body mass despite clinical recovery. Other indices of lean body mass also tended to fall with recovery so, as testosterone production had increased in the recovery phase, it seemed that this anabolic steroid had not influenced changes in lean body mass. Problems with isotope equilibrations were encountered in these particular patients and it was concluded that results of isotope dilution studies should be interpreted with caution in abnormal metabolic states.

Osteoporosis as a consequence of low testosterone was investigated. A study elsewhere had described abnormal pituitary fossa x-ray appearances in patients with chronic obstructive airways disease, the changes being ascribed to the raised intracranial pressure of hypercapnia. Our study confirmed these abnormalities but they were more prevalent among normocapnic pink puffers than hypercapnic blue

bloaters. Moreover porotic rather than erosive changes were identified and it was postulated that low anabolic steroid production in these patients may contribute to the bony abnormalities.

A correlation between red cell volume and the degree of hypoxia was confirmed in these patients. Such secondary polycythaemia causes increased blood viscosity resulting in decreased peripheral blood flow and we were able to show that cerebral blood flow is diminished to a similar extent in both primary and secondary polycythaemics. Improved cerebral blood flow occurred with venesection but this did not change the serum testosterone levels thus indicating that sluggish cerebral circulation is not a cause of the hypothalamic depression. Despite increase in cerebral blood flow cerebral oxygen delivery fell after venesection. Thus it was concluded that caution is required with venesection in secondary polycythaemic patients.

A final study recently completed has shown that in hypoxic respiratory patients supervised continuous oxygen therapy improves testosterone production and also pituitary release of luteinising and follicle-stimulating hormones. Unfortunately such oxygen therapy tends to be impracticable over prolonged periods.

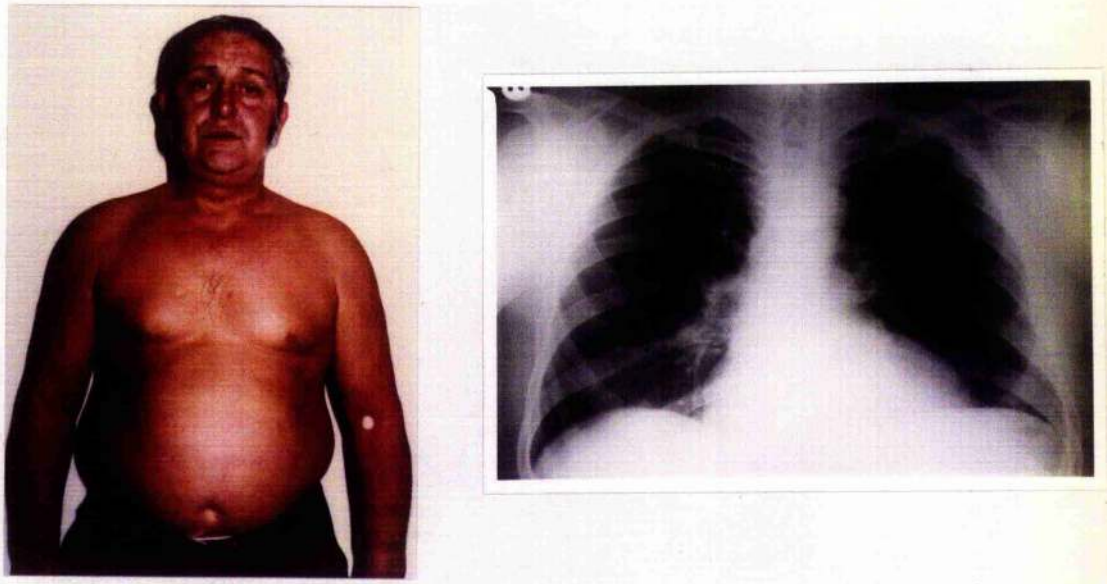
Certain implications of our findings are discussed. As yet the effect of testosterone replacement on libido, sexual performance, body habitus and osteoporosis has not been tested. The finding of low sex hormone production and sexual impotence in hypoxic lung disease may add valuable fuel to antismoking compaigns.

PREFACE

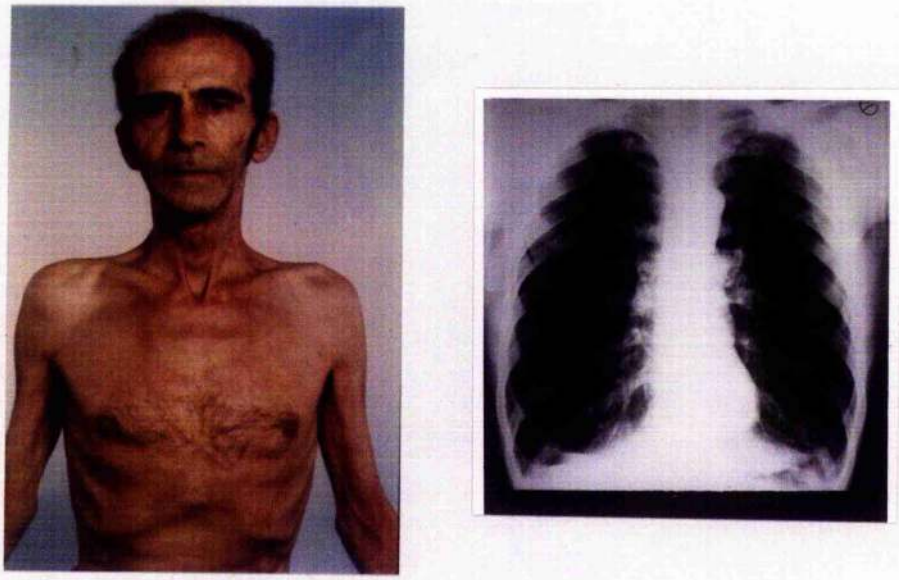
It was at the Southern General Hospital, Glasgow in 1974 while working with Dr Gavin Shaw that my interest in respiratory medicine was nurtured by Dr Robert Cuthbert. Soon it became clear that in Glasgow chronic bronchitis and emphysema, sometimes together called chronic obstructive airways disease, was an especially common condition. After moving to Dundee as respiratory registrar at King's Cross Hospital and Ninewells Hospital it was evident that despite the fairer climate in the East, chronic bronchitis and emphysema was similarly prevalent. By 1975 I was feeling an urge to be involved in research in this field although it seemed well trodden at least as far as physiology and pathology were concerned. However I recalled that one of my chiefs and mentors had said: "when you're stuck, stand back and take a fresh look at the overall picture".

When one stands back and looks at patients with chronic obstructive airways disease (COAD) two distinct syndromes are recognised[1]. Respiratory physicians refer to the first as the "blue bloater" (figure 1). He has smoked for most of his life, is short necked, thick chested and somewhat overweight. He is florid and somewhat cyanotic, dyspnoeic on exertion and hypoventilates at rest. There is productive cough, hypoxia and hypercapnia with a resultant tendency to secondary polycythaemia, pulmonary hypertension and cor pulmonale failure. Chest x-ray shows no obvious hyperinflation but a broad heart shadow and signs of pulmonary arterial hypertension. Pathologically as well as having histological evidence of chronic bronchitis there is centriacinar emphysema, the periphery of each acinus being spared.

His contrasting counterpart is called the "pink puffer" (figure 1). He is also a cigarette smoker but is underweight with spare build, long chest and neck and thin non-cyanotic features. He is breathless on exertion and hyperventilates at rest but has less cough and spit



Clinical and chest x-ray appearance of 'blue bloater'



Clinical and chest x-ray appearance of 'pink puffer'

Figure 1

than his blue bloater counterpart. He retains relatively normal blood gases till late in the disease. Chest x-ray shows hyperinflation with a low diaphragm and a long narrow heart shadow in marked contrast to that of the blue bloater. Histologically there is less chronic bronchitis while emphysema is panacinar. That weight loss is a feature of panacinar emphysema has been demonstrated for some time[2] and this has been shown to be almost invariable when the condition is associated with alpha-1-antitrypsin deficiency[3] which is an autosomal recessive condition predisposing homozygotes to emphysema. In my Scottish series[4,5] which will be described in Chapter II this condition will be described in some detail.

The two syndromes described above, pink puffers and blue bloaters represent the extreme ends of the spectrum of chronic obstructive airways disease and it has seemed to many physicians that there must be distinct, as yet unrecognised differences in their metabolism to explain the extraordinary contrast in body habitus. It is also possible that these syndromes are genetically predetermined though it has not been part of my project to study this aspect. The initial projects (Chapters IV and V) were designed to identify metabolic, endocrine or nutritional differences between the groups.

CHAPTER I

METHODS

RESPIRATORY SYMPTOMS AND PHYSIOLOGY

Criteria for COAD and severity of dyspnoea were those defined by the Medical Research Council[6,7]. Spirometry was performed using a Vitalograph spirometer with the patient sitting, the best of three attempts being selected. Results of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and forced expiratory volume/forced vital capacity ratio (FEV_1/FVC %) were compared with normal values[8]. Airways obstruction was deemed to be present when the FEV_1 was less than 70% of predicted normal value and FEV_1/FVC ratio less than 70%. From the spirometry curve the forced expiratory flow rate between 75 to 85% of vital capacity (FEF 75-85%) was obtained[9]. Closing volume (CV) and closing volume/vital capacity ratio (CV/VC%) were measured by the nitrogen method[10]. The maximum mid-expiratory flow rate (MMFR) was obtained from a flow volume curve[11]. Measurement of total lung capacity (TLC) was measured by the helium dilution method[12] and transfer factor (TF) by the single-breath technique[13]; values were compared with predicted normal[14,15]. Patients with pulmonary fibrosis were deemed to have restrictive lung disease where FEV_1/FVC ratio was more than 70%, TLC less than 80% of normal and TF less than 80% of normal. Arterial blood gas samples were taken from the radial artery with the patient lying rested for 15 minutes prior to sampling unless otherwise stated in the text. Heparinised samples were capped and put on ice. Estimations were performed within

10 minutes of sampling using Clark PO_2 and Severinghaus PCO_2 electrodes (IL 313).

BIOCHEMISTRY

Plasma urea and electrolytes and serum iron, total iron binding capacity (TIBC), vitamin B_{12} and red cell folate, urinary d-xylose and faecal fat estimations were made using standard laboratory techniques. Serum alpha-1-antitrypsin was measured by a commercial immunodiffusion technique (M-Partigen; Behring Institute) and alpha-1-antitrypsin phenotypes were determined as described by Cook[16]. Serum tri-iodothyronine (T_3), thyroxine (T_4), 17 hydroxyandrogens (testosterone), dehydroepiandrosterone (DHA), dehydroepiandrosterone sulphate (DHAS), androstenedione, oestradiol, follicle stimulating hormone (FSH), luteinising hormone (LH), growth hormone (HGH) and urinary aldosterone were measured by radioimmunoassay. Serum cortisol was measured by a fluorometric method and urinary 17-ketosteroids spectrophotometrically. Prolactin was measured by radioimmunoassay as described by Cowden et al[17] and TSH by the method of Hall et al[18]. Pituitary stress tests involved the injection of insulin (0.2U/kg) and measuring serum HGH and cortisol in blood samples taken at standard time intervals (0',30',60') and also the injection of thyrotrophin releasing hormone (TRH, 200µg) and gonadotrophin releasing hormone (GnRH, 100µg) (Relefact LH-RH/TRH, Hoechst) and measuring serum TSH, prolactin, FSH and LH in blood samples taken at standard time intervals (0',30',60'). All endocrine studies were performed at approximately the same time of day (10.30am-12midday). Laboratory normal data for all these methods had been obtained from appropriate volunteer and hospital inpatient populations.

METABOLIC AND RADIONUCLIDE STUDIES

Red cell volume (RCV) and plasma volume (PV) determinations were performed by administering ^{51}Cr labelled red cells and ^{125}I labelled human serum albumin and measuring the radioactivity in venous blood samples 10,20 and 30 minutes after injection. Predicted normal values were calculated using the equation developed by Nadler and colleagues[19] and modified by Hume and Goldberg[20]. Total body water (TBW) and extracellular water (ECW) were measured by administering first tritium (^{3}H) - labelled water and later bromine-77 or bromine-82 intravenously and analysing venous samples four hours after injection[21]. Intracellular water (ICW) was obtained by subtraction, levels being compared with predicted normal values[22]. Dry body weight was deduced by subtracting TBW from body weight. Fat-free mass (FFM) was estimated by four different methods: (a) from triceps and subscapular skinfold thickness[23]; (b) from total body water[24]; (c) from total body potassium (TBK)[25]; (d) predicted from height and weight[26]. TBK values were obtained by measuring the naturally occurring radionuclide potassium-40 using a shielded room whole body monitor described by Runcie and Hilditch[27]. The results obtained were compared with predicted values calculated using height, weight and age[25]. Red cell potassium was deduced from a modification of the method of Hald[28].

RADIOLOGY

Chest x-rays were taken using routine methods with standard radiographic equipment and coned lateral radiographs of the pituitary fossa were made with a high-definition technique described by du Boulay[29].

STATISTICS

Correlations between indices (eg, figure 6) were in all cases tested by a least sum of squares linear fit. Statistical comparisons between groups of values were made using either Student's t test, Wilcoxon's rank test, Wilcoxon's test for paired differences or the chi-square test. On each occasion the statistical method used is appended to the appropriate table.

CHAPTER II

REVIEW OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

This brief review of the history and pathology of chronic bronchitis and emphysema may serve to familiarise the non-respiratory clinician and non-clinical reader with these conditions.

The definition of a chronic bronchitic as applied in Britain is "a patient who has coughed up sputum daily for at least three consecutive months for more than two consecutive years". This definition was drawn up by the Medical Research Council in 1965[6] after many years of confused diagnostic criteria. 'Primary emphysema' on the other hand exists where there is little cough or spit but gross breathlessness[30]. In both conditions there is airways obstruction which is caused in chronic bronchitis by a combination of factors which include occlusion by mucus of the bronchial lumen, thickening of the mucosa, increased bronchial muscle tone and distortion of airways by fibrosis. In both conditions but predominantly in emphysema premature closure of airways also results from loss of the tissue elasticity which normally holds the airways open. Such chronic airways obstruction, which can be assessed by the simpler respiratory function tests, is usually only partly reversed by bronchodilator drugs as compared with asthma where obstruction may be intermittent and almost completely reversible. In their individual pure forms chronic bronchitis and emphysema represent the extreme ends of a spectrum of disease collectively termed chronic obstructive airways disease (COAD).

Prevalence of chronic bronchitis in Britain in middle-aged men nears twenty per cent[31] and it is one of the most common causes of loss of work. Consequent mortality, higher in males and in those of lower socioeconomic groups[32], compares unfavourably with that in other countries. In recent years there has been some decline in prevalence and mortality in this country[33] partly reflecting a reduction in smoking and atmospheric polution[34] but sadly the reduction in cigarette consumption so far seems only to apply to males[35].

Smoke itself causes bronchoconstriction but in addition leads to hypertrophy of bronchial mucus-secreting glands and inhibition of ciliary action. These together cause retention of mucus which encourages infection. Cigarette smoke also enhances elastase release from polymorphonuclear leucocytes[36] and depresses the antibacterial activity of alveolar macrophages[37] and these factors may contribute to the pathogenesis of emphysema. There is no firm evidence of a hereditary factor apart from alpha-1-antitrypsin deficiency, one cause of primary emphysema which accounts for a very small proportion of patients with COAD. This aspect will be covered in more depth at the end of the chapter.

With prolonged smoking, resultant bronchial narrowing, mucosal swelling and secretion retention, superadded infection results[38]. Normal columnar epithelium may become squamous in type and fibrosis of the walls of small airways leads to more permanent narrowing. Chronic bronchitis is usually accompanied by secondary emphysema which is characterised by air spaces (acini) distal to the terminal bronchioles becoming enlarged from dilatation or by destruction of alveolar walls possibly related to increased levels of or unopposed action of elastase, Though initially the centre of

the acinus is affected (centriacinar emphysema) in time the whole acinus may be involved[39] although panacinar emphysema is more characteristic of primary emphysema. Disintegration of alveolar walls results in destruction of capillaries and reduction in the capillary bed with consequent increase in pulmonary arterial pressure and hypertrophy of pulmonary arterioles.

Reduction in alveolar ventilation produces retention of carbon dioxide (CO_2), the arterial CO_2 tension ($PaCO_2$) rises and arterial oxygen tension (PaO_2) falls. These abnormalities are manifested initially when the patient has an exacerbation of his clinical problem associated with a chest infection but in time some patients will develop sustained chronic hypoxia and hypercapnia. Such bouts of hypoxia lead to vasoconstriction of pulmonary arterioles which causes a rise in pulmonary artery pressure and right ventricular hypertrophy (cor pulmonale)[40]. Peripheral oedema often ensues and the reasons for this, which will be explained in later chapters, are complex and not solely related to right heart failure. Such patients, usually of endomorphic build, are commonly referred to as 'blue bloaters'. The onset of cor pulmonale in such COAD patients is taken as a poor prognostic sign, two-thirds of patients dying within five years of its appearance[41]. 'Pink puffers' on the other hand, who tend to be ectomorphs, have emphysema predominantly and manage to maintain near normal arterial blood gas tensions till the terminal stages of the disease at the cost of a major respiratory effort.

Pulmonary function tests play an important role in the detection of early obstructive airways disease and are also of value in assessing progress or deterioration. They have some place in assessing prognosis and also in determining the efficacy of various

drug therapies. The reader may wish to refer here to the Glossary of terms on page 4. FEV_1 is the amount of air which can be expelled in one second and this represents 70-80% of FVC in normals. Reduction of the FEV_1/FVC ratio indicates obstruction to expiration. The FEV_1 is easily measured and correlates well with the other simple test of airways obstruction using the peak expiratory flow meter (PEFR)[6]. The FEF 75-85%[9] which is obtained from the spirometry curve (Vitalograph) and the CV[10] which is a measure of small airways closure are used to detect early preclinical airways obstruction mainly in epidemiological studies. The MMFR has a similar place[11]. Overinflation of the lungs can be determined by measuring static lung volumes[12] which include the residual volume (RV) being the amount of air left in the lungs after a maximal voluntary expiration. An elevated RV and a high RV/TLC ratio indicates air trapping. Conversely low values indicate loss of lung volume as in pulmonary fibrosis. Transfer factor[13] which is classically low in pulmonary fibrosis is often well preserved in airways obstruction though it is usually low in patients with pronounced emphysema[42].

It would seem that COAD is a largely preventable disease and despite recognition of the aetiological factors in most countries it still remains a major challenge to preventative medicine[35]. Treatment involves the long term management of the patient and also clinical care of exacerbations. Affected patients who continue to smoke should be actively discouraged as stopping may halt or at least slow the disease process[43,44]. However even in well organised anti-smoking clinics long term results are not very encouraging[45]. Continuous antibiotic therapy seems to have little influence on the course of the disease[46] and it is more

usual to treat infective exacerbations promptly as they arise. Bronchodilator drugs may afford considerable relief but the improvement in FEV_1 along with reversibility of bronchospasm varies very much from patient to patient. Corticosteroids are occasionally helpful but prolonged use should be instituted only after specialist objective assessment. The role of physiotherapy and mucolytic agents is more controversial.

Acute exacerbations of bronchitis may be mild in the early stages and respond readily to an antibiotic course. In later attacks dyspnoea may require the addition of bronchodilator drugs usually given orally or by pressurised aerosol but in more severe cases requiring hospital admission these drugs are administered often systemically and by inhalation via a nebuliser system or by intermittent positive pressure machine often combined with skilled physiotherapy to aid expectoration. Hypoxic patients will require carefully monitored oxygen therapy till the PaO_2 on breathing air attains its pre-exacerbation level. Excessive concentrations of inhaled oxygen are notoriously dangerous to these patients as, due to the presence of chronic hypercapnia, the respiratory centre depends on hypoxia for stimulus. Cor pulmonale failure may respond to antibiotic and oxygen therapy alone but resistant oedema will require diuretic therapy. Digoxin is rarely useful in this situation. Exacerbations tend to become progressively more severe and respiratory stimulants with high dose corticosteroids are used as a last resort. It is during such attacks that patients die, usually of respiratory failure and such an outcome can often be predicted in the long term by monitoring the FEV_1. For example when the FEV_1 value falls below 0.75 litres the five years mortality is 67% or greater[47].

More recently the role of continuous domiciliary and ambulatory oxygen therapy in hypoxic COAD subjects has been assessed[48,49]. Such oxygen therapy reduces haematocrit in secondary polycythaemic patients[49] and pulmonary arterial pressure in those with cor pulmonale[50]. Recently a Medical Research Council trial has shown reduced mortality with such oxygen therapy given over five years to such patients[49]. However it requires to be given for at least 15 hours each day and must raise the PaO_2 to above 8.0kPa (60mmHg) to be of benefit[49-51]. So in view of this and the large numbers of potentially treatable cases huge costs are involved. Not surprisingly there is poor compliance and few patients use the oxygen for more that 15 hours per day[51].

In view of the fact that only some who smoke develop chronic bronchitis and emphysema it would seem possible that genetic factors contribute. However there is no firm evidence of such a factor apart from alpha-1-antitrypsin deficiency and this accounts for a very small proportion of all emphysema cases, being first described by Laurell and Eriksson in 1963[52]. The antitrypsin anomaly is inherited as an autosomal recessive characteristic, homozygotes and heterozygotes being distinguished from normal individuals by estimation of serum enzyme levels. Various phenotypes are described the more usual ones being ZZ=homozygous, MZ=heterozygous and MM=normal[16]. Homozygous individuals, who comprise 1 in 3450 of the UK population[16], have a strikingly high incidence of emphysema but whether heterozygous subjects are more prone to lung disease is debated[3,53,54]. The identification of a number of homozygotes stimulated the author to study their families and report the first Scottish series[4] as well as the first autopsy illustrated British cases[5].

ALPHA-1-ANTITRYPSIN DEFICIENCY AND CHEST DISEASE[4]
A CLINICAL AND PHYSIOLOGICAL STUDY

Four families with alpha-1-antitrypsin deficiency were identified. Of seven homozygous subjects five smoked and had chest disease while the two non-smokers were unaffected. Productive cough was a feature in four of the five affected homozygotes and symptoms commenced earlier than is usual with chronic bronchitis and emphysema. Of 11 heterozygous subjects only five who smoked had symptomatic or laboratory evidence of obstructive airways disease, in each case less marked than that of their homozygous smoking relatives. Severely affected subjects were underweight, the degree of weight loss being related to the measured severity of obstructive airways disease.

PATIENTS

Four index cases in the series, summarised in table 1, were identified in Dundee and Glasgow teaching hospitals. They were suspected of having the deficiency because of relative youth at onset of symptoms, severity of symptoms or radiographic basal distribution of emphysema while homozygous alpha-1-antitrypsin deficiency was confirmed by measuring the serum level. Subjects were deemed homozygous with a serum alpha-1-antitrypsin level in the low range (7-15% of mean normal; 260-560mg/l) and heterozygous if in the intermediate range (30-65% of mean normal; 1120-2440mg/l)[55]. A total of 23 available close relatives of the index cases had their serum enzyme level measured. Subjects were weighed and measured and percentage of predicted weight calculated[56].

An additional survey was performed to determine the prevalence of alpha-1-antitrypsin deficiency amongst patients with emphysema. Sixty-nine subjects comprising both ward and chest clinic patients with chronic bronchitis and emphysema were screened for the deficiency. The presence of emphysema was identified clinically and confirmed

Clinical features and pulmonary function tests in homozygous alpha-1-antitrypsin deficient subjects

Case no.	Sex	Age (years)	Weight (%pred)	Cigarettes (pack years)	Cough & spit (years)	Dyspnoea (grade)	Dyspnoea (years)	FEV_1 (%pred)	FEV_1/FVC (%pred)	FEV_1/FVC (%)	TF (%pred)
1*	M	56	73	10	10	4	20	17	46	33	34
2*	M	37	84	20	20	3	6	28	55	43	31
3	F	19	115	2	3	3	2	93	79	69	94
4*†	M	35	73	10	0	3	7	16	37	29	28
5†	M	35	108	0	0	1	-	107	97	77	79
6	M	39	96	0	0	1	-	86	92	71	93
7*‡	M	42	73	10	20	4	15	12	46	35	N.D.

* = Index case

† = Non-identical twins

‡ = Deceased

N.D. = Not done

Table 1

radiographically by an independent observer applying the criteria of Laws and Heard[57].

RESULTS

From the 23 close relatives of the four index cases screened for the enzyme deficiency three further examples of homozygous affection were identified, one (No 5) being a non-identical twin of the index case No 4. Eleven examples of apparent heterozygous affection were also identified among the relatives and table 3 shows their relationship to the respective index cases.

In the enzyme screening survey of 69 random emphysematous patients one example of homozygous deficiency was found in a terminally ill man aged 43 years (No 7) in addition to seven patients with apparent heterozygous affection (not included in tables 1-3).

All four index cases were or had been smokers and had developed pulmonary symptoms in their third or fourth decade (table 1). Though case Nos 2 and 4 continued to smoke, Nos 1 and 7 had stopped because of chest symptoms. Case No 7 had stopped in his twenties but despite this there had been a relentless deterioration in his condition culminating in death from respiratory failure at age 42 years. One homozygous relative, No 3 who smoked developed respiratory symptoms one year after commencing the habit. Two non-smoking homozygous subjects (Nos 5 and 6) were free of pulmonary symptoms. Dyspnoea from a relatively early age was the most distressing feature of affected homozygotes. Case No 3 had intermittent bronchial asthma which was aggravated by exertion and relieved by salbutamol aerosol. She was non-atopic on skin testing. Of the heterozygotes (table 2) the four who smoked were the only ones with respiratory symptoms but these tended to occur later in life than with homozygotes.

Clinical features and pulmonary function tests in heterozygous alpha-1-antitrypsin deficient relatives of the 4 homozygous index cases

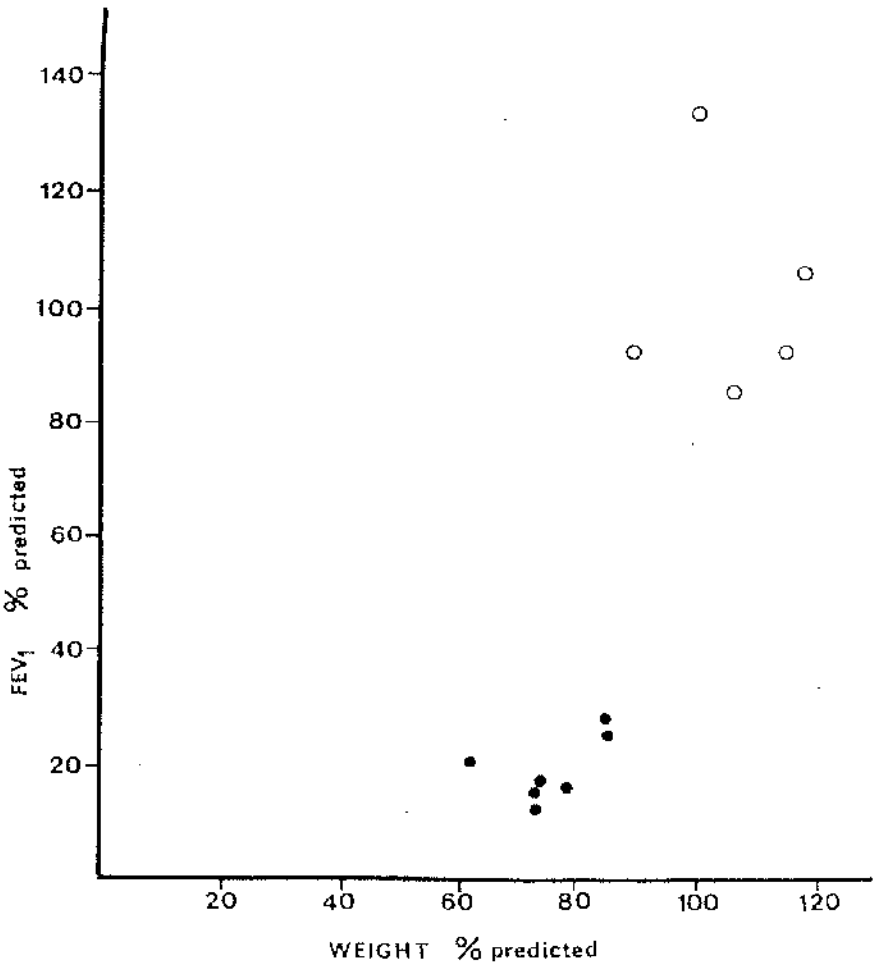
Case	Sex	Age (years)	Weight (%pred)	Cigarettes (pack years)	Cough & spit (years)	Dyspnoea (grade)	Dyspnoea (years)	FEV_1 (%pred)	FEV_1/FVC (%pred)	FEV_1/FVC (%)
8	M	55	88	25	2	1	-	103	110	79
9	M	24	98	0	0	1	-	128	96	80
10	M	19	99	0	0	1	-	108	98	82
11	F	27	100	0	0	1		130	96	82
12	M	29	94	13	8	1	-	116	91	74
13	F	17	96	0	0	1	-	131	101	89
14	F	36	94	20	15	1	-	94	92	76
15	M	60	87	200	35	3	13	32	100	69
16	F	56	92	0	0	1	-	138	100	77
17	M	67	95	0	0	1	-	97	109	73
18	F	37	121	0	0	1	-	110	106	87

Table 2

FEV_1 was very low in all index cases (table 1) but the other homozygous subjects were not substantially affected. TF was very low in the three affected homozygous subjects tested. Case No 15 who had been a very heavy smoker for many years was the only heterozygous subject to have a low FEV_1 (table 2). It can be seen from figure 2 that homozygous smokers with emphysema as well as having very low FEV_1 values are thin with weights between 60-85% of predicted normal values while non-smoking non-emphysematous siblings with normal FEV_1 values have weights near their normal predicted values. Though numbers are small there is an obvious and significant difference between the two groups and an evident association between panacinar emphysema and weight loss.

In subjects with a relatively normal FEV_1 the more sensitive tests of early airways obstruction, FEF75-85%, MMFR and CV were performed (table 3). Subject No 3, a young smoking homozygote, appeared to have early airways obstruction in that the FEF75-85% and MMFR levels were lower and the CV/VC ratio higher than predicted. The non-smoking homozygote case No 6 had a normal FEV_1 and FEV_1/FVC ratio but again there was evidence of early airways obstruction by the above criteria. However although considered a non-smoker he admitted to an occasional cigarette at social functions. Heterozygous smoking subjects Nos 8,12 and 14 had reductions in FEF75-85% and MMFR suggesting early obstructive airways disease but in each case CV/VC ratio was less than the predicted value which is a normal finding. Non-smoking heterozygotes appeared to be unaffected though subject No 10 had a high CV/VC ratio.

In the survey of 69 patients with chronic bronchitis and emphysema only one (case No 7 above) had a serum alpha-1-antitrypsin level in the homozygous range. Seven others had levels in the



Comparison of weights of seven emphysematous alpha-1-antitrypsin deficient subjects with those of five of their non-smoking, non-emphysematous siblings. Emphysematous (●) and unaffected (O) subjects: Significance of weight difference between groups, $p < 0.01$.

FIGURE 2

Sensitive tests of obstructive airways disease in alpha-1-antitrypsin deficient subjects with grossly normal FEV_1 measurement

Case no.	Antitrypsin level	Relationship to index case*	Smoker/ non-smoker	FEF 75-85% (%pred)	MMFR (%pred)	CV/VC (%pred)	CV/VC (%)
3	Homozygous	2S	S	59	43	202	17.0
5	"	4S	NS	93	92	75	9.8
6	"	4S	NS	47	58	116	16.8
8	Heterozygous	1S	S	89	91	59	12.0
9	"	1C	NS	154	96	86	7.6
10	"	1C	NS	99	89	121	8.5
11	"	1C	NS	115	79	31	3.3
12	"	2S	S	72	84	64	7.0
13	"	2S	NS	115	134	-	0
14	"	2S	S	48	50	78	10.5
16	"	2P	NS	103	88	98	18.8
17	"	4P	NS	78	99	64	16.0
18	"	4S	NS	90	130	96	13.0

* = Number indicates index case related to: P = Parent of index case, S = Sibling, C = Child
(Note case 15 = 2P)

Table 3

heterozygous range but none showed characteristically basal radiographic appearances to distinguish them from the rest of the survey patients nor was there evident difference in age of onset of severity of symptoms. Height and weight measurements were available in 38 of the 61 subjects with normal serum alpha-1-antitrypsin levels (28 males, 10 females; age range 38-67; average 58 years). Weight as a percentage of predicted weight for sex, height and age ranged between 58 to 97 per cent with an average of 75.3 per cent. For the heterozygous group (6 males, 1 female; age range 50-82; average 64 years) predicted weight ranged between 65 to 87 per cent with an average of 76.4 per cent.

DISCUSSION

This small survey suggests that heterozygous subjects are not affected differently from those with normal levels of the enzyme. It confirms a low prevalence of homozygous deficiency in a random population with chronic bronchitis and emphysema though it is likely to be higher in a population of emphysematous patients without chronic bronchitis, so called primary emphysema. Indeed where disabling symptoms commence under the age of 40 years and when basal emphysema is apparent radiographically under the age of 50 years the proportion of patients with the deficiency is much greater[53]. Dyspnoea, the most common symptom[58], started under the age of 40 years in the five affected homozygotes in this series. As chest radiographs may remain normal in this condition till the fourth decade asthmatic symptoms in the non-atopic, as in case No 3, should arouse suspicion[59,60].

Homozygotes who smoke are likely to develop emphysema and those without respiratory symptoms are in the main non-smokers[2,54]. Cases

No 4 and 5 are the first homozygous alpha-1-antitrypsin deficient twins to be described. Albeit non-identical, they demonsrate with remarkable clarity the contrast in symptoms, lung function and body weight between the affected smoker and the non-affected non-smoker.

Though Welch and colleagues[3] claimed that emphysema is primary in type in affected homozygotes, productive cough at least in Britain is a feature of about half such cases[2]. Weight loss has previously been thought to be characteristic of this enzyme deficiency[3] but as pointed out by Hutchison and colleagues[2] and as further shown so clearly in this survey it is an expected finding in primary emphysema and is not specific for alpha-1-antitrypsin deficiency.

Sensitive tests of obstructive airways disease (FEF75-85%, MMFR, CV/VC) appear to show in this series at least that non-smoking homozygotes may have early disease (table 3, case No 6) and that even at the age of 19 years a smoking homozygote can have early obstructive change (case No 3). They also demonstrate that non-smoking heterozygotes have no such changes and that smoking heterozygotes as compared with smoking homozygotes seem relatively protected. Only heterozygote case No 15 had a substantial reduction in FEV_1 but dyspnoea had started in the fifth decade and was less severe than in homozygous subjects. Certainly any increased tendency to develop emphysema amongst heterozygotes is not marked which would indicate that genetic counselling of homozygous subjects is not of vital importance. However screening of their siblings has value as anti-smoking informed advice can be given to the homozygous.

WIDESPREAD PANACINAR EMPHYSEMA WITH ALPHA-1-ANTITRYPSIN DEFICIENCY - NECROPSY FINDINGS IN TWO PATIENTS[5]

The clinical, laboratory and necropsy findings in two patients with homozygous alpha-1-antitrypsin deficiency who smoked illustrate the accelerated deterioration seen in this form of emphysema. Though emphysema usually appears on x-ray to be more marked in the bases in this condition, whole lung sections obtained in these two patients suggest that this is not necessarily so.

INTRODUCTION

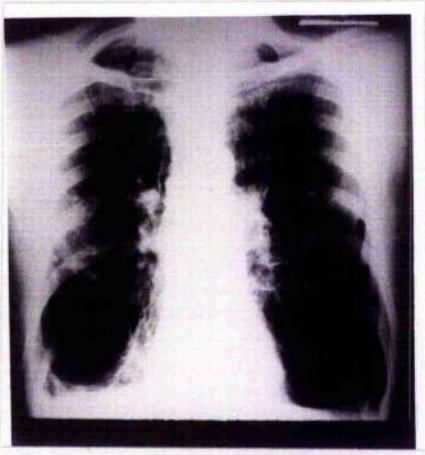
Homozygous alpha-1-antitrypsin deficiency occurs in as many as 48% of subjects with severe primary emphysema under 50 years of age[53]. There are reports in the world literature of post-mortem data[55,61,62] but few in the British literature[63] and all stress a basal distribution of emphysema.

CASE 1

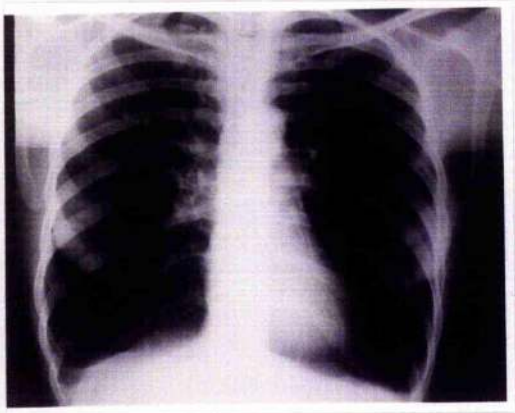
A 37-year-old housewife was admitted urgently with breathlessness, lassitude and ankle swelling. She had smoked 20 cigarettes daily for 20 years till several months before admission when she stopped because of symptoms. There had been productive cough for seven years and progressive breathlessness over the previous two years. A diagnosis of homozygous alpha-1-antitrypsin deficiency (phenotype ZZ) had been made before admission.

On examination she was drowsy, cyanosed and produced clear sputum. There was clinical cor pulmonale failure. She weighed 41.3kg which was 78% of her predicted weight. A chest radiograph showed predominantly basal emphysema (figure 3).

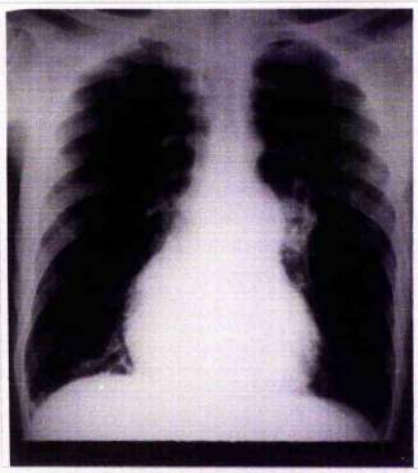
Investigations: FEV_1 0.38 litres, FVC 0.94 litres and FEV_1/FVC 40% (predicted 2.3 litres, 2.6 litres and 88% respectively); PaO_2



Chest x-ray of patient with alpha-1-antitrypsin deficiency showing typical basal distribution of emphysema with appearances suggestive of bullae.



Chest x-ray of case 1 with alpha-1-antitrypsin deficiency showing predominantly basal distribution of emphysema.



Chest x-ray of case 2 with alpha-1-antitrypsin deficiency showing widespread emphysema, pulmonary arterial hypertension and enlarged heart.

Figure 3

3.8kPa (29mmHg), $PaCO_2$ 10.5kPa (79mmHg).

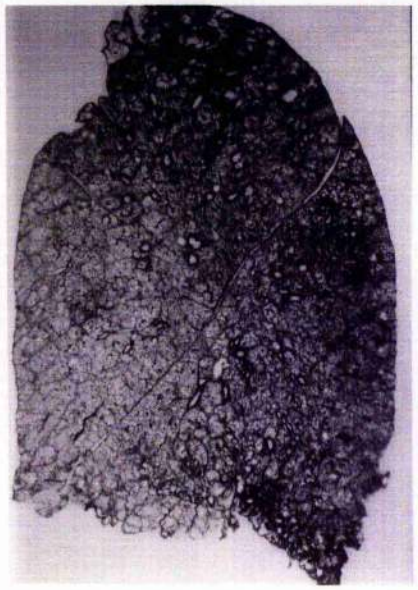
The illness was managed as an exacerbation of bronchitis with respiratory failure. Despite standard treatment she deteriorated and died four days after admission.

Autopsy was performed 18 hours after death. The heart weighed 280g (normal range for height and sex 259±30g)[64] with marked right ventricular hypertrophy, the right ventricle weighing 87g (normal <80g)[65]. The pulmonary artery showed flecks of atheroma. The voluminous lungs showed air trapping. Whole lung sections were prepared by the technique of Gough and Wentworth[66] and showed severe widespread panacinar emphysema (figure 4). Histology of major bronchi showed only mild hypertrophy of mucus glands. The liver weighed 900g (normal range 1200-1500g)[67], the cut surface showing chronic venous congestion but no cirrhosis. Histology showed multiple PAS-staining diastase-resistant globules within periportal hepatocytes (figure 5) consistent with alpha-1-antitrypsin deficiency[68]. Small bowel histology showed normal villous pattern.

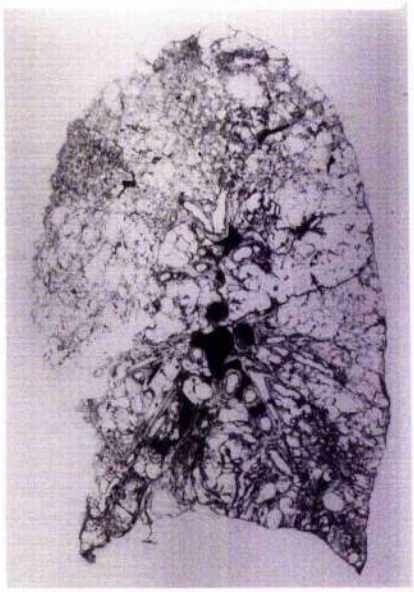
CASE 2

A 42-year-old man was admitted to hospital as an emergency with breathlessness, ankle swelling and drowsiness. He had smoked 20 cigarettes daily for eight years but had stopped in his early twenties with productive cough. He worked as a labourer in the building trade until breathlessness at rest had forced him to give up work nine years before admission.

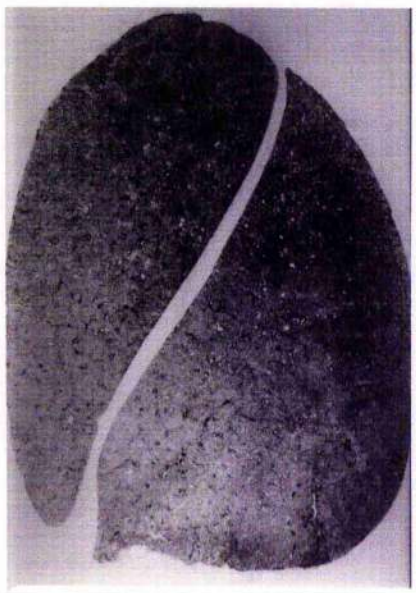
Clinically he was drowsy and cyanosed with purulent sputum and cor pulmonale failure. He weighed 52kg which was 73% of his predicted weight. The chest radiograph (figure 3) was reported as showing widespread emphysema, pulmonary arterial hypertension and a moderately



A Whole lung section of case 1 with alpha-1-antitrypsin deficiency showing severe widespread panacinar emphysema.

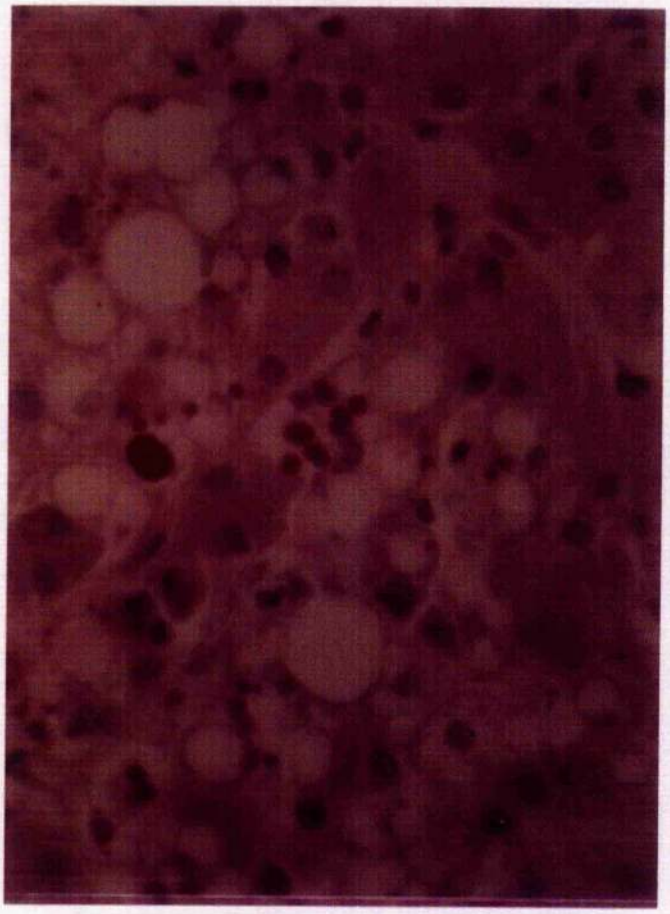


B Whole lung section of case 2 with alpha-1-antitrypsin deficiency showing severe widespread panacinar emphysema



C Whole lung section from normal subject for comparison with A and B

Figure 4



Histological appearance of liver from case 1 showing multiple PAS-staining (red) diastase-resistant globules within periportal hepatocytes characteristic of alpha-1-antitrypsin deficiency.

Figure 5

enlarged heart.

Investigations: FEV_1 0.4 litres, FVC 1.15 litres, FEV_1/FVC 34% (predicted 3.35 litres, 4.1 litres and 82% respectively); PaO_2 4.2kPa (32mmHg), $PaCO_2$ 7.9kPa (60mmHg); haemoglobin 16.5g/dl, haematocrit 0.51.

The illness was managed as chronic bronchitis and emphysema with cor pulmonale and super-added infection leading to right heart failure. Oxygen (Ventimask 24%), frusemide, potassium supplements, intramuscular ampicillin and high doses of corticosteroids were given. There was a good diuresis and his condition had improved after one week.

Further investigations after treatment: PaO_2 5.1kPa (39mmHg), $PaCO_2$ 5.4kPa (41mmHg); haemoglobin 18.3g/dl, haematocrit 0.61; red cell mass 2.3 litres, plasma volume 1.9 litres, blood volume 4.2 litres (predicted 1.6, 2.0, 3.9 litres). In view of the increased red cell mass two separate venesections of one unit of blood were performed. His condition gradually deteriorated and he died of respiratory failure five weeks after admission. Alpha-1-antitrypsin phenotype was reported as ZZ after death.

Autopsy was performed 40 hours after death. Significant findings were confined to the heart, lungs and liver. The heart weighed 500g (normal range 317±40g) with right-sided dilatation and right ventricular hypertrophy. Both lungs were heavy, the right weighing 900g (normal 450±80g)[69] and the left 880g (normal 400±90g). The right lung was inflated and fixed in formalin after which whole lung sections showed widespread panacinar emphysema (figure 4). Dissection of left bronchi revealed mucopus and histological examination showed patchy pneumonia. Sections of bronchi showed anthracotic deposits, chronic inflammatory cells and mild increase in mucus secreting glands. The liver weighed

only 1070g (normal range 1200-1500g) and the cut surface showed marked chronic venous congestion which was confirmed histologically. There was no evidence of cirrhosis. Many of the hepatocytes contained multiple diastase-resistant PAS positive granules.

DISCUSSION

Incapacitating symptoms usually start in the fourth decade of life in emphysematous patients which alpha-1-antitrypsin deficiency[2] and these two cases are typical of this premature disability. The cough and spit and histological changes of chronic bronchitis seen here are usual features of the syndrome[61,62] though the emphysema is generally classified as primary[3,70]. Weight loss is also typical[2,3] although it is also a feature of emphysema without alpha-1-antitrypsin deficiency[71]. Though villous atrophy has been found in association with alpha-1-antitrypsin deficiency[63,72] it was excluded in case 2 as a cause of weight loss by post-mortem small bowel histology and in case 1 by antemortem jejunal biopsy. Cirrhosis was absent in both cases despite liver weights being low conforming with the general experience that it is not usual for the emphysema and cirrhosis of alpha-1-antitrypsin deficiency to coexist[68].

A rise in haemoglobin and haematocrit after diuresis, as in case 2, is in our experience not uncommon during treatment of cor pulmonale failure presumably due to unmasking of secondary polycythaemia.

Previous reports emphasise the distribution of emphysema as most advanced in the lower zones both radiographically[70,73] and at post-mortem[55,62]. In case 1 the radiograph appeared to show predominantly basal emphysema but this was not so in case 2

(figure 3). In both our cases whole lung sections showed emphysema to be severe and widespread (figure 4). The lungs of case 2 were heavy and possibly the presence of oedema and widespread pneumonia masked the usual radiological appearance. Bullae were not seen in sections from either patient nor have they been demonstrated in previous illustrated post-mortem studies[55,62] despite radiological impressions of basal bullae in this condition (figure 3). We suspect that 'bullae' reported radiologically in this condition are often avascular areas of severe panacinar emphysema.

In conclusion the cases demonstrate the typical clinical course of emphysema due to alpha-1-antitrypsin deficiency. The post-mortem findings were similar to the few previous illustrated published studies but both our patients appeared to have more widespread distribution of panacinar emphysema than is usual in this condition.

This rare enzyme deficiency arouses considerable interest. It demonstrates that some people are genetically predisposed to develop emphysema and it may well be that other genetic factors will be discovered. More interestingly from the point of view of this thesis, both of these patients showed the marked weight loss almost invariably seen in the end stages of primary emphysema. Such cases stimulated my interest in the metabolic and endocrine aspects of COAD both of which I suspected must be disordered in such a catabolic state. The relevant literature of these aspects is reviewed in Chapter III.

CHAPTER III

REVIEW OF THE LITERATURE

This review summarises relevant literature prior to 1977 when the first projects (Chapters IV and V) were undertaken. A number of ideas were developed as a result of the findings of the initial studies and the subsequent research projects in this thesis followed in logical sequence. The literature relevant to these projects, often comparatively recent, will be reviewed in the introduction to each section. This review may be considered as an introduction to the pilot studies (Chapters IV and V).

The classical descriptions of 'pink puffers' and 'blue bloaters' described in the introduction are frequently encountered in clinical practice and though predetermined genetic factors might seem a likely explanation why one group of smokers should develop one syndrome and another group should develop the other, the genetic markers in each group have not been compared. Genetic differences or not, conventional theories of body build suggest that such a wide range of body habitus is likely to be associated with some difference in caloric intake, absorption of food, aspects of metabolism or hormone production. To date no studies of these factors have been made when comparing pink puffers and blue bloaters. However there has been some work related to weight loss in emphysema and a considerable amount of research into hypoxia of high altitude.

Weight loss in emphysema is well described[4,5,74-6] and according to Vandenbergh and colleagues[74] its onset is a poor prognostic sign, preceding the onset of cor pulmonale by about two years and often being a premonitory sign of death within a few years. Weight loss also occurs in acute exposure to high altitude[77-82]

mainly as loss of fat[79] but also of protein[80,81]. Such weight loss in both situations can be impressive. As much as 20 percent or more of body weight in emphysema[74] and 20 pounds loss after eight months at altitude in excess of 18,000'[82] has been noted.

The causes of such profound changes in body habitus in both these situations has been debated. Depressed appetite has been noted in emphysema[74,83], in which situation Thurlbeck found an increased prevalence of peptic ulcers[84], and also in men acutely exposed to high altitude hypoxia[77,78,82,85] though in the latter situation Nair and Prakash claimed that cold rather than hypoxia was responsible[86]. In emphysema Wilson and colleagues[83] found that emphysematous subjects with weight loss ingested significantly less calories than those who did not lose weight. However as in Vandenbergh and colleagues' study[74] there was great individual variation and some subjects who lost weight ate more than their non weight losing counterparts. Though Pugh[82] noted anorexia in a Himalayan expedition it was concluded that this was not the sole reason as the subjects still ate high calorie meals. Malabsorption of food has been considered as a cause of weight loss in emphysema as Milledge[87] found decreased xylose absorption in hypoxic patients with congenital heart disease and with COAD. This abnormality was reversed after administering oxygen for only eight hours. Though this might represent true malabsorption of xylose, hypoxia could influence such results by affecting xylose metabolism. Milledge concluded that such apparent malabsorption of carbohydrate could explain weight loss in emphysema though in a physician's experience the most hypoxic subjects are not necessarily those who are underweight and of course we see hypoxic overweight blue bloaters and less hypoxic underweight pink puffers.

Jejunal villous atrophy associated with weight loss has been described in emphysema associated with alpha-1-antitrypsin deficiency[72] and also with extrinsic allergic alveolitis[88,89] but it seems probable that the gastrointestinal abnormality in these conditions is related to the basic enzyme or immunological fault. At altitude Pugh[82] noted that there was a tendency to bulky greasy stools and he postulated decreased fat absorption. Another explanation for such weight loss is the energy cost of breathing in dyspnoeic conditions[90] though Pugh[82] found normal basal metabolic rates in men exposed to high altitude who lost weight. However others[91] have noted basal metabolic rates to be increased at altitude.

Conceivably endocrine abnormalities might be causally related to the variation in body habitus seen in COAD and rapid loss of body mass found at high altitude. There have been comparatively few endocrine studies of COAD subjects and certainly these parameters have not been compared in pink puffers and blue bloaters. However Marmorston and colleagues[92] found reduced urinary 17-ketosteroid (17-KS; metabolite of testosterone) concentrations in emphysematous subjects suggesting decreased testosterone secretion and the authors concluded that "an abnormality in hormone excretion in pulmonary emphysema suggests that hormonal or metabolic factors may be involved in the pathogenesis of this disease". The possibility that such hormone abnormalities could be a result of rather than a contributary factor in the development of this disease was not discussed. Urinary metabolites of cortisol were normal in emphysematous patients in Marmorston's study and the hypothalamo-pituitary-adrenal axis has also been found to be normal in COAD by other workers[93]. Corticosteroid production appears to be normal

in high altitude natives also[94,95]. However with acute exposure to high altitude increased production of urinary 17-hydroxycorticosteroids (17-OCHS; metabolites of cortisol) occurs in animals[96] and in men[97-101] though these values return to normal after a few days. This may be a non-specific reaction to stress though Klain and Hannon[78] suggested that the surge in corticosteroid output could cause the prompt weight loss seen with acute exposure to high altitude by a catabolic effect.

Despite the fact that COAD is commonly encountered in hospital practice there has been much more assessment of endocrine function at high altitude hypoxia (either real or simulated) than in hypoxic lung disease. Ayres and colleagues[102] found in subjects exposed to altitudes in excess of 15,000' for 24 days that aldosterone secretion fell profoundly with resultant sodium loss and potassium retention and high total body potassium (TBK) levels. These findings were similar to those of Hogan and colleagues[103] and Slater and colleagues[104-6] who found that aldosterone secretion fell to 65 percent of mean control value. This is considered by some to be the explanation for the low prevalence of systemic hypertension in high altitude natives though Ward[107] points out that low rather than high TBK levels also have been found in high altitude experiments. Antidiuretic hormone (ADH) levels fall in men exposed to high altitude[108] and to artificial experimental hypoxia[101]. Such a drop in ADH may account for the increased water turnover noted at altitude by Pugh[82] who found urinary output increased by 45 percent at altitude though he felt that increased fluid loss from the lungs caused by hyperventilation contributed to the elevated water turnover.

There has been little if any work investigating growth hormone (HGH) levels in hypoxic COAD. Circumstantial evidence suggests this

hormone may be disordered by hypoxia at altitude as the growth of high altitude Peruvian natives is delayed and termination of growth does not occur till the age of 20-22 years[109]. Sutton and colleagues[110] found they had elevated levels of HGH which suggested that increased production was required to maintain acclimatisation by facilitating organ hypertrophy and enhancing erythropoietin release. They also found elevated HGH levels in low altitude natives who were stressed in a hyperbaric chamber to simulate high altitude conditions[111].

With regard to sex hormones in COAD apart from the demonstration by Marmorston and colleagues[92] of reduced levels of urinary 17-ketosteroids in their emphysema subjects suggesting diminished testosterone production in that situation there seems to have been little other work. At acute exposure to high altitude reduction in urinary 17-ketosteroids suggesting low testosterone secretion has been noted by several workers[82,97,100,112] though the natives retain comparatively normal levels[94,113]. Such low testosterone production has been associated with low luteinising hormone (LH) levels which suggests either hypothalamic or pituitary rather than primary testicular suppression[114] and it is noteworthy that pituitary concentrations of LH and FSH are altered in rats exposed to high altitude[115]. Alteration of sex hormones may be responsible for the delayed menarche in Peruvian women[116] and also there is evidence of reduced fertility at these high altitudes. Oligospermia, reversed by migration to the lowlands[116] at harvest time, was considered by James[117] to be due to a physiological effect of altitude. Certainly there is good evidence that fertility in animals is reduced at high altitude, the germinal epithelium undergoes changes, and in particular more rams with lower sperm counts are required to cover the same number of ewes than at low altitude[118]. It is of interest

that the birth of the first Spaniard at a high village in Peru (14,500') did not occur till 53 years after their arrival and was hailed as something of a miracle! There is however no literature on the sexual potency of men or more detailed assessment of sex hormones and sex function at altitude. Nor is it known whether disturbance of sex hormones affects male fertility in COAD. Indeed in this field there has been only scant reference to sexual dysfunction[119].

Body potassium, which would be expected to be abnormal at high altitude and in COAD because of changes in body mass and aldosterone status, has been studied in both situations. It has been shown by Ayres and colleagues[102] to increase along with a fall in aldosterone production after acute exposure to high altitude though according to Ward[107] this area is confused as others have shown decreased total body potassium values at altitude. Confusion also exists in COAD where studies have shown low TBK values when using isotope dilution methods[75,120-3] but normal values using a whole body monitor according to Howie and colleagues[124] who considered the discrepancy was due to insufficient equilibration time used in isotope dilution studies[125]. Certainly the hyperaldosteronism which is taught as a feature of cor pulmonale failure might be expected to cause low TBK and this area requires further research.

Red cell volume (RCV) is increased in high altitude natives and polycythaemia may in some cases become excessive[126]. It may develop fairly quickly, as in Pugh's study[82] a mean haemoglobin of 20.5g/100ml was noted after 40 days at 18,000'. A fall in plasma volume at high altitude[82,127] contributes to the degree of polycythaemia. Hume and colleagues[128] found that among patients with COAD and high haematocrits there was a correlation between arterial oxygen tension (PaO_2) and RCV

and that the response was similar in degree to that of normal individuals living at high altitude. He also found[129] that as at high altitude low plasma volumes occurred in COAD patients with secondary polycythaemia and this was not related to diuretic therapy. Red cell volume measurement rather than haematocrit alone therefore is important when assessing polycythaemia in these situations. Other studies have not confirmed the relationship between PaO_2 and red cell volume in COAD[130] and the reasons for this are unclear.

In chapters IV and V we describe two studies which attempted to clarify certain areas outlined in this review of the literature.

CHAPTER IV

PILOT STUDIES

POTASSIUM STUDIES IN CHRONIC OBSTRUCTIVE AIRWAYS DISEASE[131]

Low total body potassium, as distinct from normal serum and red cell potassium values, is frequently found in each type of COAD, especially with acute exacerbations of cor pulmonale. Such depletion of potassium stores may indicate tissue loss.

INTRODUCTION

Studies of body potassium measuring exchangeable potassium by an isotope dilution method after the administration of potassium-42 have shown that gross potassium depletion may occur in patients suffering from chronic airways obstruction[75,120-3]. Possible reasons for low potassium values include anorexia or poor diet, increased urinary loss due to hyperaldosteronism, hypoxia-induced "sick-cell syndrome" where intracellular sodium is higher and intracellular potassium lower than normal[132], and loss of tissue mass resulting from hypoxia in acute exacerbations[75]. Campbell and colleagues[75], however, did note that these potassium values remained low even when their patients had recovered from cor pulmonale for two to three months and had regained body weight.

In contrast to isotope dilution studies Howie and colleagues[124] using a whole body monitor found normal values of total body potassium in 12 patients who had previously had acute respiratory failure with cor pulmonale but who at time of study were in remission. This discrepancy was considered to be due either to exchangeable potassium being a smaller fraction of body potassium in patients with COAD than in normal subjects or due in part to insufficient equilibration time used in isotope dilution studies[125].

We report a study carried out to reassess the state of TBK in patients with chronic obstructive airways disease using a whole body monitor and to determine any differences in TBK between patients with normal and those with high arterial carbon dioxide tensions.

METHODS

Seventeen men with COAD who were chest clinic attenders were selected to give a wide distribution of body habitus from frankly underweight to obese. A modified Medical Research Council questionnaire[133] on respiratory symptoms was applied, and in all cases grade 3 (stop for breath while walking at own pace on level ground) or grade 4 (breathless at rest) dyspnoea had been present for more than one year. All but one were past or present cigarette smokers, and only one was free from cough or sputum. Spirometry was performed; forced expiratory volume in one second (FEV_1) was always less than 70% of predicted normal value, and forced expiratory volume/forced vital capacity ratio (FEV_1/FVC%) was always less than 70% signifying airways obstruction (table 4). No patient had blood urea concentration greater than 10mmol/l. All were in remission and without cardiac failure, and medicinal treatment was continued during the study. Patients were grouped according to arterial carbon dioxide tensions ($PaCO_2$), those with a $PaCO_2$ level greater that 5.8kPa hereafter being referred to as the "hypercapnic group" and those with a level less than 5.8kPa as the "normocapnic group".

A further two male patients (No 18 and 19) who had been admitted in respiratory failure and in severe cor pulmonale were similarly studied as soon as right heart failure had cleared.

Patients were admitted to a metabolic investigation unit for three days. Height and weight were measured, and the latter was

Potassium studies - Laboratory results of patients with chronic obstructive airways disease grouped according to $PaCO_2$ values

Patient	Age (years)	Height (metres)	Weight (kg)	FEV_1 (% predicted)	FEV_1/FVC (%)	PaO_2 (kPa)	$PaCO_2$ (kPa)	Red cell volume (measured / predicted)%	Plasma volume (measured / predicted)%
Hypercapnic ($PaCO_2$ >5.8kPa)									
1	70	1.55	66.9	68.0	61.8	8.1	5.9	143	98.0
2	53	1.70	98.0	26.6	40.5	7.2	6.4	157	106.1
3	66	1.59	84.4	30.9	41.5	7.2	6.0	134	88.2
4	66	1.65	76.0	28.6	38.8	5.3	9.0	165	93.7
5	48	1.67	72.7	28.8	43.9	8.2	6.4	88	83.4
6	59	1.58	67.7	34.0	68.0	6.2	7.9	159	96.4
7	52	1.69	79.6	54.8	54.0	7.4	5.9	141	104.9
8	69	1.81	52.6	25.0	25.7	6.3	7.6	103	115.5
Mean	60.4	1.66	74.7	37.1	46.8	7.0	6.9	136	98.3
Standard deviation	8.5	0.083	13.4	15.6	13.7	0.99	1.15	27.5	10.3
Normocapnic ($PaCO_2$ <5.8kPa)									
9	38	1.83	57.4	24.4	42.2	7.7	5.1	96	93.9
10	70	1.61	37.8	28.3	44.2	9.8	4.7	86	99.5
11	56	1.55	41.2	26.0	30.9	8.4	4.7	124	122.2
12	48	1.64	50.0	8.4	45.1	7.4	5.7	118	122.5
13	53	1.64	54.6	48.4	40.0	7.5	5.3	118	89.4
14	52	1.69	46.3	29.7	47.6	8.2	5.3	107	104.8
15	56	1.64	42.2	20.0	33.7	9.8	5.1	110	78.3
16	61	1.64	54.4	22.6	48.7	8.0	5.2	120	107.6
17	57	1.73	80.0	66.7	51.9	9.6	5.3	105	91.6
Mean	54.6	1.66	51.5	30.5	42.7	8.49	5.15	111.6	101.1
Standard deviation	8.8	0.08	12.6	17.1	6.9	0.99	0.31	13.3	14.8
Significance of difference between the means*	NS	NS	P<0.01	NS	NS	P<0.01	P<0.01	P<0.05	NS

See glossary for explanation of abbreviations in all tables; NS = Not significant

* = Statistics using Student's t test

Table 4

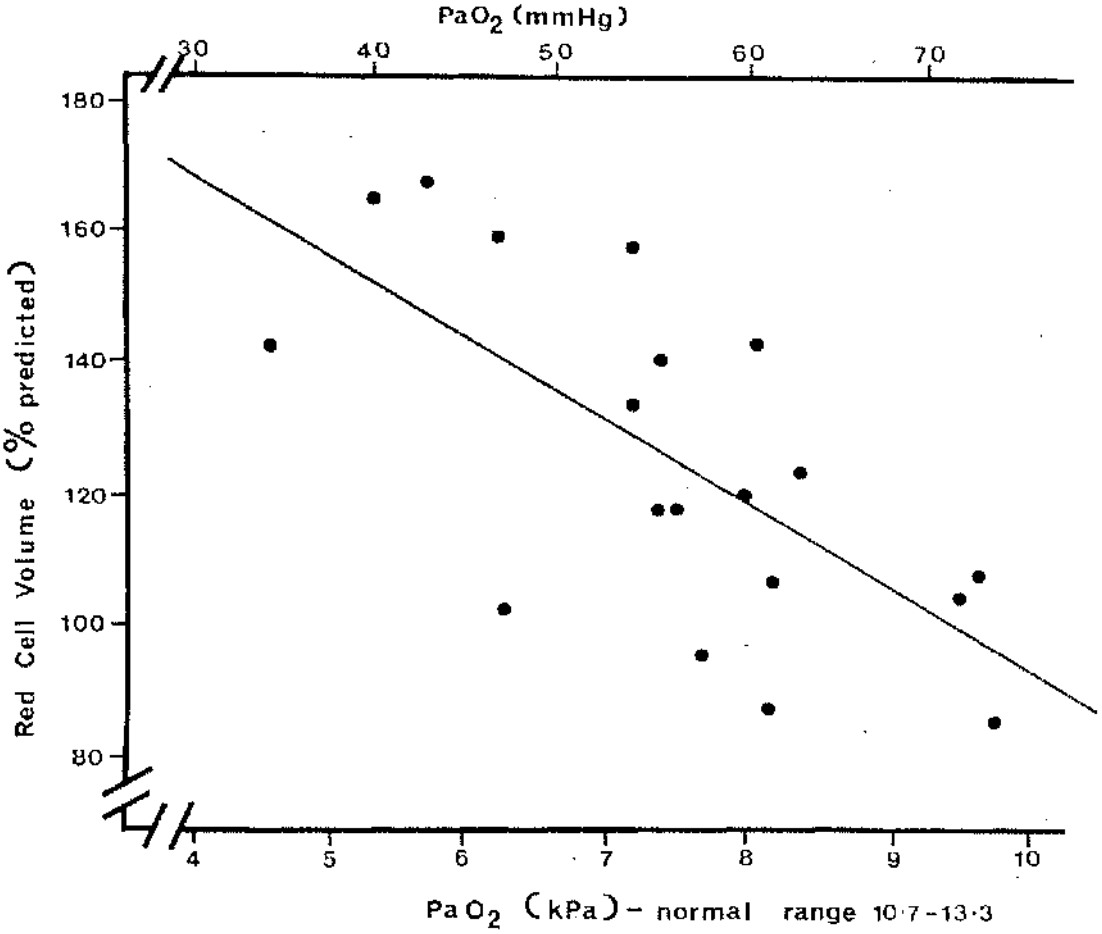
compared with that predicted for sex, height and age[56]. A chest radiograph was obtained and examined by a radiologist who awarded an "emphysema score"[134]. An arterial blood sample for blood gas estimation was taken on each of two consecutive days from the radial artery with the patient lying rested and breathing room air for 30 minutes. The average of the two results was used.

Red cell volume (RCV) and plasma volume (PV) determinations were performed and predicted normal values were calculated. TBK values were obtained and on the same day red cell potassium was deduced and serum potassium measured.

RESULTS

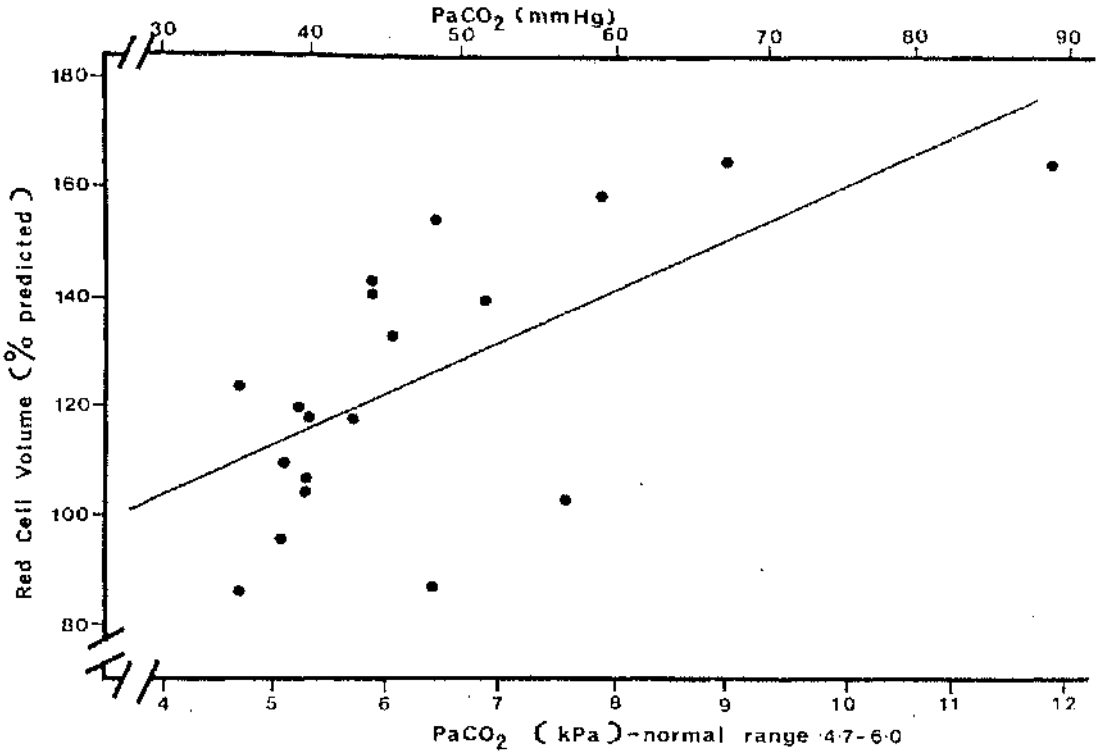
There was no significant difference in age, height, or spirometric readings between the two groups of subjects separated according to $PaCO_2$ values (table 4). The hypercapnic group of eight patients was significantly heavier and had a lower arterial oxygen tension and higher RCV expressed as a percentage of predicted normal. Considering the 17 patients individually there was a significant inverse relationship between level of PaO_2 and red cell volume ($p<0.01$) (figure 6) and a significant direct relationship between level of $PaCO_2$ and red cell volume ($p<0.01$) (figure 7).

Serum potassium values were always normal, and there was no difference between the two groups in serum or erythrocyte potassium. Two patients (2 and 8) in the hypercapnic group (table 5) had significantly low values of TBK (TBK 79.1% and 77.8% of predicted normal; $p<0.005$) as had the two additional cor pulmonale patients (18 and 19) (table 6). The mean value of TBK in the normocapnic group was significantly lower than normal, though that for the hypercapnic group was not. The difference between the mean values of TBK in the two groups (90.2% and 95.0%) was not significant. The



Correlation between arterial oxygen tension and red cell volume in 19 patients with COAD ($r=0{\cdot}684, p<0{\cdot}01$).

FIGURE 6



Correlation between arterial carbon dioxide tension and red cell volume in 19 patients with COAD ($r=0{\cdot}652, p<0{\cdot}01$).

FIGURE 7

Potassium studies including total body potassium of patients with chronic obstructive airways disease grouped according to $PaCO_2$ values

Patient	Serum potassium (mmol/l)	Erythrocyte potassium (mmol/l)	TBK (mmol)	TBK (predicted)	TBK (measured / predicted)%	Emphysema score* (0-32)	Diuretic
Hypercapnic							
1	4.8	105.2	2680	2450	109.4	16	-
2	3.6	102.4	3095	3913	79.1†	23	Frusemide 40mg, Slow-K
3	3.9	96.8	3125	2926	106.8	23	-
4	3.8	105.9	2647	3056	93.2	24	Frusemide 40mg, Slow-K
5	4.2	89.4	2849	3261	87.3	23	Frusemide 40mg, spironolactone 100mg
6	4.2	106.8	3036	2639	115.0	ND	Frusemide 40mg
7	3.3	102.6	3183	3483	91.4	ND	-
8	4.6	114.6	2350	3020	77.8†	26	-
Mean	4.05	103.0	2896	3094	95.0	22.5	
Standard deviation	0.50	7.4	279	464	14.0	3.4	
Normocapnic							
9	3.9	102.0	3235	3583	90.3	21	-
10	5.3	111.9	1926	1959	98.3	25	Amiloride 5mg, hydrochlorthiazide 50mg
11	4.1	101.7	2023	2012	100.2	22	-
12	4.3	96.6	2386	2616	91.2	23	-
13	5.1	104.9	2309	2665	86.6	19	-
14	3.8	97.0	2304	2675	86.1	26	-
15	5.0	107.0	1910	2325	82.2	25	-
16	4.4	105.6	2120	2552	83.1	ND	Bendrofluazide 2.5mg with k
17	3.8	104.0	3452	3668	94.1	18	-
Mean	4.41	103.4	2408	2672	90.2†	22.4	
Standard deviation	0.58	4.8	560	602	6.4	2.9	
Significance of difference between the means ‡	NS	NS	P<0.05	NS	NS	NS	

* = Sutherland et al 1971[34]

† = Significantly low; $p<0.005$

‡ = Statistics using Student's t test

ND = Not done

Table 5

Various laboratory results including total body potassium values in two patients recently recovered from severe cor pulmonale

Patient	Age (years)	Height (metres)	Weight (kg)	FEV_1 (%pred)	PaO_2 (kPa)	$PaCO_2$ (kPa)	Red cell volume (measured / predicted)%	Plasma volume (measured / predicted)%
18	42	1.65	55.8	12.3	4.7	6.7	144	83
19	78	1.59	99.7	15.0	5.7	11.9	167	119

Patient (continued)	Serum potassium (mmol/l)	Erythrocyte potassium (mmol/l)	TBK (mmol)	TBK (predicted)	TBK (measured / predicted)%	Diuretic
18	4.9	96.8	2026	2880	70.3%*	Frusemide 40mg, Slow-K
19	5.1	101.0	2376	3297	72.5%*	Frusemide 40mg, Slow-K

* = Significantly low; $p<0.005$.

Table 6

degree of potassium depletion in these 17 stable COAD patients was not apparently related to diuretic treatment (table 5). There was no significant correlation between the severity of emphysema as measured by the emphysema score and the level of TBK, though the more severely depleted patients tended to have a higher emphysema score (table 5).

The validity of the equation for predicting normal TBK values[25] was checked in the whole body monitor by measuring TBK in 18 normal male volunteers, and the mean measured values were within 99.8% of predicted normal (99.83±7.32).

DISCUSSION

As potassium concentrations are much higher in cells than in extracellular fluid any loss of tissue mass is associated with a consequent drop in body potassium. Campbell and colleagues[75] noted that patients lost weight during exacerbations of cor pulmonale and that this weight loss was associated with a fall in exchangeable potassium, which rose again when weight was regained in remission though it remained lower than normal. Emphysematous patients also lose weight[4,5,74-6,135] though often retaining normal arterial blood gas tensions. Such a fall in tissue mass might be expected to be associated likewise with a drop in TBK. Hence the decision to compare two groups of patients; underweight emphysematous patients with relatively normal arterial blood gases and their overweight hypercapnic counterparts.

The 17 patients, all with stable COAD, had incapacitating dyspnoea. Both groups (table 4) were similar with respect to age, height, and spirometry, but the hypercapnic group had a lower mean PaO_2 value, were of heavier build, and had an abnormally high

mean RCV as compared with the normocapnic group. Harrison and colleagues[130] have pointed out that where secondary polycythaemia is present in COAD there is a correlation between arterial oxygen tension and RCV but that not all chronically hypoxic COAD subjects develop polycythaemia. Hume[128] also showed that in 15 COAD patients with polycythaemia there was a correlation between PaO_2 and RCV and that the RCV response to hypoxia in COAD was similar to that of normal individuals living at high altitude. Moreover the same author[136] demonstrated that in patients with acute exacerbations of chronic bronchitis with respiratory failure and cor pulmonale, an individual's "steady state" PaO_2 could be predicted from the red cell volume. Our 19 patients were not selected on the grounds of elevated haematocrit and it would seem from our finding that in a random population of COAD patients there is indeed a correlation between PaO_2 and RCV though it is our impression also that occasional individuals with chronically low PaO_2 values may not develop polycythaemia. Why they may not is unclear.

The mean TBK level in the normocapnic group was significantly low, though no individual had a significantly low value. In the hypercapnic group three patients (2,5, and 8) had low levels of TBK though the mean value for this group as a whole was not significantly low. Patient 2 had spent two weeks in hospital with severe cor pulmonale two months previously, had responded well to diuretics, and by the time of measurement was free of oedema. Patient 8, on the other hand, although treated at home four weeks previously for a severe exacerbation of dyspnoea associated with chest infection, had not had frank cor pulmonale in more than a year. In the case of patient 5, the TBK value was low, though not significantly, and he, like patient 2, had been in hospital four

months previously with severe cor pulmonale. The remainder of the 17 patients had been free from cor pulmonale for more than one year.

In view of the finding of low TBK values in three hypercapnic patients, patients 18 and 19 were studied additionally some 10 days after they were admitted to hospital with severe cor pulmonale, which by this time had settled (table 6). Their very low values of TBK confirmed that potassium depletion can occur in patients recovering from cor pulmonale, as previously shown by Campbell and colleagues[75]. Howie and colleagues[124] showed normal values of TBK in patients recovered from cor pulmonale but did not state for how long they had been in remission. In our series all the patients on diuretics (table 2) had in the past had manifest cor pulmonale, but most did not have significantly low potassium values when measured.

Of the four patients (2,8,18 and 19) with significantly low TBK values three (2,8, and 19) had higher than normal PV's (tables 4 and 6), suggesting that in fact latent cardiac failure may have been present[128] giving rise, because of increased extracellular fluid, to falsely low values of TBK as a percentage of predicted for height, weight and age. TBK values did not seem to correlate inversely with PV in other patients, however, nor did they relate to diuretic therapy (table 5). It may be that in those patients recently recovered from severe cor pulmonale, gross diuresis as well as loss of tissue mass contributes to potassium depletion, though Dargie and colleagues[137] showed that frusemide without potassium supplements was not associated with a lowering of TBK.

Red cell potassium, usually well preserved and not a good indicator of intracellular potassium values in general, was normal in both groups and was not low in the subjects with significantly

low TBK (table 5). This finding conforms with that of Boddy and colleagues[138], that in normal subjects red cell potassium values are not related to TBK values and our findings of normal serum potassium values even where TBK is severely depleted reinforces those of other workers[123].

This study confirms that TBK may in fact be low in COAD, that weight loss may be responsible, and that the diuretic phase of treated cor pulmonale may contribute.

CHAPTER V

PILOT STUDIES

DIET, ABSORPTION AND HORMONE STUDIES IN RELATION TO BODY WEIGHT IN OBSTRUCTIVE AIRWAYS DISEASE[139,140]

The considerable differences in body weight between the blue bloaters and pink puffers cannot be explained by variation in calorie intake or dietary absorption. Major alterations in anabolic steroid status were found to occur with low serum testosterone levels apparently related to hypoxia. Blue bloaters had lower serum levels than the pink puffers of both testosterone and the adrenal androgen dehydroepiandrosterone while pink puffers had higher serum dehydroepiandrosterone levels than controls.

INTRODUCTION

Whereas patients with chronic obstructive airways disease who are chronic bronchitics tend to be overweight, those with predominant emphysema lose weight and tend to be thin[4,5,74-6]. Depressed food intake has already been shown to occur only in a proportion of these thin emphysematous subjects[74,83]. Malabsorption is a possible factor as this has been described in emphysema with alpha-1-antitrypsin deficiency[72] and also in association with the weight loss of altitude hypoxia[82] although in this condition appetite suppression does occur. A high prevalence of gastrointestinal disturbances in COAD has been cited as a possible cause of poor appetite[74] while yet another factor contributing to the weight loss may be the increased energy expenditure of dyspnoeic breathing[90].

Depression of gonadal function occurs at altitude[82,97,100,112] and though endocrine studies in COAD have been remarkably few one paper[92] comparing endocrine function of bronchial carcinoma patients with that of emphysematous and normal subjects demonstrated lower urinary 17-ketosteroid (metabolite of testosterone) production in

emphysematous subjects compared with the other groups. It was considered that this abnormality might be causally related to the development of emphysema but not that it might be a consequence of emphysema.

As for the reasons for weight loss in emphysema are far from clear we have sought to determine the relation of diet and absorption of food to body habitus in COAD and have also studied the hormonal aspects of two groups of patients with obstructive airways disease - hypercapnic, hypoxic chronic bronchitic "blue bloaters" and their thin emphysematous normocapnic "pink puffer" counterparts.

PATIENTS

Sixteen stable male chest clinic patients were chosen to represent a wide range of body habitus. Most of the patients had also participated in the earlier body potassium study[131] (Chapter IV) and fulfilled similar clinical and pulmonary function criteria for COAD. Having been selected by these criteria, arterial blood gas tensions were then measured. They were grouped according to arterial carbon dioxide tensions ($PaCO_2$), those with a $PaCO_2$ level greater than 5.8kPa hereafter being referred to as the "hypercapnic group" and those with a level less than 5.8kPa as the "normocapnic group".

Subjects were admitted to a metabolic unit for three days. Food consumption was assessed by experienced dieticians and converted to a caloric value[141] which was then compared with the individual's predicted normal value[142]. Similar dietary assessments for comparison were made in 18 men admitted with various traumatic orthopaedic problems but who were otherwise healthy. In addition the eight underweight subjects underwent jejunal biopsy, estimation of serum iron, B_{12}, and red cell folate as well as d-xylose (5g)

excretion test and three-day faecal fat estimation to assess intestinal absorption.

Blood was taken at midday from patients on the second day of admission. Serum tri-iodothyronine (T_3), thyroxine (T_4), 17 hydroxyandrogens (testosterone), dehydroepiandrosterone (DHA), oestradiol, luteinising hormone (LH), follicle-stimulating hormone (FSH), prolactin, cortisol and urinary aldosterone values were measured.

Control values for these hormones were taken from a group of 14 male patients without chest disease matched for age attending either an anticoagulant clinic or with treated pernicious anaemia at a haematology clinic.

RESULTS

There was no significant difference in age, height, or spirometric readings between the two groups of subjects separated according to $PaCO_2$ values (table 7), but the hypercapnic group of eight subjects was significantly heavier (hypercapnic mean weight 78.0kg; normocapnic 51.7kg; $P<0.01$). Seven of the eight hypercapnic subjects were overweight and seven of the eight normocapnic subjects underweight. The hypercapnic group had lower arterial oxygen tensions and higher red cell volume expressed as a percentage of predicted normal.

Five of the overweight and seven of the underweight subjects ingested less than their predicted calorie requirement (table 8), and there was no significant difference between the two groups in mean daily calorie intake. On average both groups ingested more but not significantly more than the healthy men. Daily protein intake was normal and similar in each group as were the serum T_3 and T_4

Diet and hormone studies - Laboratory results of patients with chronic obstructive airways disease grouped according to $PaCO_2$ values

Subjects	Age (yr)	Height (m)	Weight (% predicted)	FEV_1 (% predicted)	FEV_1/FVC (%)	PaO_2 (kPa)	$PaCO_2$ (kPa)	Red cell volume (measured / predicted %)
Hypercapnic ($PaCO_2$ >5.8kPa)								
1	69	1.81	64.2	25.0	25.7	6.3	7.6	103
2	70	1.55	108.5	68.0	61.8	8.1	5.9	143
3	53	1.70	133.3	26.6	40.5	7.2	6.4	157
4	66	1.59	132.5	30.9	41.5	7.2	6.0	134
5	66	1.65	111.8	28.6	38.8	5.3	9.0	165
6	78	1.59	161.1	40.1	50.8	5.6	11.9	167
7	59	1.58	104.2	34.0	68.0	6.2	7.9	159
8	52	1.69	110.0	54.8	54.0	7.4	5.9	141
Mean	64.1	1.65	115.7	38.5	47.6	6.7	7.6	146.1
Normocapnic ($PaCO_2$ <5.8kPa)								
9	38	1.83	70.7	24.4	42.2	7.7	5.1	96
10	70	1.61	57.9	28.3	44.2	9.8	4.7	86
11	56	1.55	65.4	26.0	30.9	8.4	4.7	124
12	53	1.64	79.7	48.4	40.0	7.5	5.3	118
13	52	1.69	64.0	29.7	47.6	8.2	5.3	107
14	56	1.64	61.6	20.0	33.7	9.8	5.1	110
15	61	1.64	81.0	22.6	48.7	8.0	5.2	120
16	57	1.73	106.2	66.7	51.9	9.6	5.3	105
Mean	55.4	1.67	73.3	33.3	42.4	8.6	5.1	108.3
Significance of difference*	NS	NS	P<0.01	NS	NS	P<0.01	P<0.01	P<0.01

* = Statistics using Wilcoxon's rank test

Table 7

Calorie and protein intake and thyroid function in patients with chronic obstructive airways disease grouped according to weight

Subjects	Weight (kg)	Weight (%predicted)	k calories (daily)	k calories (%predicted)	Protein (g/day)	Serum T_3 (nmol/l)	Serum T_4 (nmol/l)
Overweight							
2	66.9	108.5	2409	102.5	74	2.0	72
3	98.0	133.3	4682	161.5	118	1.6	74
4	84.4	132.5	2304	98.0	68	1.8	62
5	76.0	111.8	2746	116.9	59	1.7	72
6	101.1	161.1	2108	81.1	83	0.9	81
7	67.7	104.2	1759	67.7	53	1.8	91
8	79.6	110.0	1799	69.2	53	1.9	132
16	80.0	106.2	1388	53.4	44	1.3	51
Mean	81.7	121.0	2399	93.7	69.0	1.63	79.4
Underweight							
9	57.4	70.7	2864	98.8	102	2.1	83
10	37.8	57.9	1434	61.0	54	2.1	90
11	41.2	65.4	1854	78.9	55	1.7	71
12	54.6	79.7	2304	88.6	47	1.8	74
13	46.3	64.0	3214	110.8	87	1.7	68
14	42.2	61.6	1939	74.6	73	1.6	89
15	54.4	81.0	2231	85.8	66	1.6	84
1	52.6	64.2	2081	88.6	67	1.6	80
Mean	48.3	68.1	2240	85.9	68.9	1.78	79.9
Significance of difference *	P<0.01	P<0.01	NS	NS	NS	NS	NS
Controls-Mean			2172	83.5	70.4		
Range			1400-4460	53.8-171.5	53-96		

* = Statistics using Wilcoxon's rank test.

Table 8

values.

Serum iron levels were slightly reduced in four of the eight underweight subjects (table 9) and serum iron/total iron binding capacity (TIBC) ratio was slightly low in two. Serum B_{12} and folate and xylose excretion tests were all normal. Faecal fat was marginally elevated in one case and in another jejunal biopsy was reported as showing "slight partial villous atrophy".

All but one of our 16 COAD subjects (No 1 had a modestly raised value) had normal values for serum cortisol (table 10). The hypercapnic group had a significantly lower mean testosterone level than the normocapnic group, and both study groups had significantly lower values than the control group. Seven of the eight hypercapnic and one of the eight normocapnic subjects had serum testosterone values below the lower limit of normal. Serum DHA was lower (not significantly) in the hypercapnic group than in controls but was significantly higher in the normocapnic group than in controls. All individual values, however, were within the normal range except for subject 11 who had a raised value. Serum oestradiol, LH, and FSH were similar and normal in both groups. Serum prolactin concentrations were higher in the hypercapnic group than in both normocapnic and control groups, although the differences were not significant. However, three individual hypercapnic subjects (4,5, and 6) had raised values. Early morning urinary aldosterone levels were higher in the hypercapnic group as compared with the normocapnic group.

DISCUSSION

Interestingly, patients with COAD and with hypercapnia were overweight while those with normocapnia were decidedly underweight.

Malabsorption studies in underweight emphysematous subjects

Subjects	Serum Iron (μmol/l)	TIBC (μmol/l)	Serum Fe / TIBC (%)	Serum B_{12} (ng/l)	Serum Folate (μg/l)	Faecal fat (mmol/24hr)	Urine D Xylose (mmol/5hr)	Jejunal Biopsy (Histology)
9	24	60	40	800	3.5	13	14	Slight villous atrophy
10	24	75	32	740	6.6	14	10	Normal
11	16	54	30	1110	3.3	9	11	Normal
12	22	66	30	600	9.6	9	10	Normal
13	14	63	22	380	5.1	21	10	Normal
14	20	63	32	700	4.7	11	11	Normal
15	16	54	30	900	3.2	6	10	Normal
1	12	60	20	390	5.0	8	12	Normal
Normal range	18-36	47-72	25-50	230-950	2.7-14	<18	>8.7	-

Table 9

Results of hormone analysis in patients with chronic obstructive airways disease grouped according to $PaCO_2$ values

Subjects	Serum cortisol (nmol/l)	Serum 17 OHA (testosterone) (nmol/l)	Serum DHA (nmol/l)	Serum oestradiol (pmol/l)	Serum LH (U/l)	Serum FSH (U/l)	Early morning urinary aldosterone (nmol/l)	Serum prolactin (mU/l)	Drugs
Hypercapnic									
1	820	4.5	1.0	112	8.7	28.0	10	246	Frusemide, K, Franol
2	460	9.8	6.1	103	11.0	1.2	8	133	Nil
3	260	14.5	6.6	91	6.6	7.6	21	88	Frusemide, K, digoxin
4	400	6.7	3.5	100	8.5	3.5	7	606#	Salbutamol inhaler
5	280	7.3	4.4	ND	8.0	0.3	33	>1500#	Frusemide, K, Franol
6	460	5.0	2.1	ND	11.0	1.8	15	1030#	Salbutamol, frusemide, K, digoxin
7	280	4.3	5.0	101	15.0	6.1	39	320	Frusemide, spironolactone, digoxin
8	300	9.2	1.4	94	5.0	0.3	3	83	Nil
Mean	407	7.7†	3.8	100.2	9.2	6.1	17	501	
Normocapnic									
9	350	14.0	7.6	42	9.2	1.9	3	73	Salbutamol, chromoglycate
10	490	14.0	7.0	64	11.0	2.0	6	349	Salbutamol, Moduretic
11	550	10.0	16.2	44	7.9	2.8	4	136	Nil
12	500	15.0	6.6	123	20.0	14.0	4	188	Salbutamol, nitrazepam
13	460	15.0	5.4	121	5.3	0.3	3	135	Benylin
14	270	12.1	9.9	112	15.0	0.5	13	100	Salbutamol, Franol
15	370	17.3	11.5	89	5.3	0.3	7	121	Salbutamol, thiazide, theophylline
16	340	11.0	8.4	73	2.8	0.3	8	128	Nil
Mean	416	13.6‡	9.1$	83.5	9.6	2.3	6	154	
Significance of difference*	NS	P<0.01	P<0.01	NS	NS	NS	P<0.01	NS	
Controls-Mean		18.7	5.6	97.8	11.2	3.9		173	
-Range		9.2-27	3.3-10.8	40-150	4.0-33	0.4-12		80-286	
Normal range	225-600	11-36	0.7-13	30-200	0-33	0-23.5		60-360	

* = Statistics using Wilcoxon's rank test
† = Significantly lower than control group (P<0.01)
‡ = Significantly lower than control group (P<0.02)
$ = Significantly higher than control group (P<0.01)
\# = Individual high values

Table 10

While this finding may not be universal it supports the clinical impression of two groups of patients at the ends of a range, the hypoxic, hypercapnic, polycythaemic, overweight blue bloaters and the underweight emphysematous pink puffers with near normal arterial blood gas tensions. This study makes some new observations on the metabolic and endocrine aspects of these two groups.

Although diets have previously been assessed in emphysematous subjects losing weight, the food intake of the two groups defined here have never been compared. Within the limitations of skilled dietary assessment our results suggest that while appetite suppression may be present in individual subjects with COAD this is not universal, and indeed neither group shows a consistent alteration in eating habits (table 8). Our patients, however, were comparatively well when interviewed, and possibly dietary suppression contributes to the rapid loss of lean body mass noted during exacerbations of COAD[75]. Two previous studies[74,83] showed a significant reduction in mean calorie intake in emphysematous subjects losing weight, but in both studies there was a wide range of calorie intake between individuals and indeed some weight-losing subjects ate much more than other weight-stable subjects. This suggests some other mechanism of weight loss; a view supported by Campbell and colleagues[75] who noted from published reports that hypoxia in human altitude tests and also in laboratory animal experiments causes loss of tissue mass by an as yet unexplained process.

Though four subjects had slightly low serum iron levels the normal serum iron/TIBC ratios in six of the eight cases suggests that true iron deficiency was not present. The slightly elevated faecal fat level in one patient and mild abnormality in jejunal

mucosa in another does not amount in our view to evidence of malabsorption and we conclude that neither malabsorption nor abnormal thyroid function seem to be causative factors in the weight loss of emphysema. Another hypothetical cause of weight loss is increased calorie expenditure from the work of breathing in emphysema[90]. Weight loss however may be very rapid in exacerbations of COAD[75] yet the proportion of the matabolic rate contributed by the work of breathing is quite small.

Altitude hypoxia has been shown to depress gonadal function[82, 97,100,112] and Marmorston and colleagues[92] have drawn attention to abnormal urinary hormonal excretion patterns in emphysema. Although each of these conditions is associated with weight loss[75,82] apparently these two aspects, hormonal and metabolic, have not before been causally linked. In our study serum testosterone values were significantly low in both groups but considerably so in the hypercapnic overweight group where seven of the eight subjects had individually low values. We do not feel that age differences account for this, as appreciable reduction in testosterone does not occur till after the age of 70[143]. It is known that low testosterone values in men may cause obesity in addition to impotence, female distribution of fat and hair, and soft small testes[144]. Possibly, therefore, increased fat in these hypercapnic subjects is related to this hormonal imbalance. The reason for the normocapnic group being without excess fat is less easy to explain in such terms, although the significantly raised levels of the adrenal androgen DHA in this group compared to either the controls or the hypercapnic patients may be a factor.

In our previous paper[131] (Chapter IV) we demonstrated a correlation between PaO_2 and red cell volume though acknowledging that not all chronically hypoxic subjects develop polycythaemia.

Though why they do not is not understood it is known that in animals at least androgens have an erythropoietin stimulating effect and oestrogens a depressant action[145,146]. It appears that in man this does not apply as the more hypoxic, more androgen depleted subjects in this study were the ones who tended to be more polycythaemic.

The failure to show raised serum LH levels in the presence of low serum testosterone suggests that primary testicular failure is unlikely. Taking the 16 study subjects together there was a significant correlation between the degree of hypoxia and the reduction in serum testosterone ($n = 16$, $r = 0.600$, $P<0.05$) and also between the degree of hypercapnia and the reduction in testosterone values ($n = 16$, $r = 0.681$, $P<0.05$). Probably, therefore, hypoxia induces these changes by reducing the release of either the gonadotrophin releasing hormone from the hypothalamus or LH from the pituitary. Dynamic testing would be required to confirm this hypothesis, but interestingly in this regard hypoxia reduces antidiuretic hormone production from the human posterior pituitary[108] and at hypoxia of high altitude reduction of urinary testosterone has been associated with a fall in LH production[114].

Prolactin secretion from the pituitary is under the control of the inhibitory factor dopamine. Hyperprolactinaemia may arise in men for various reasons and may be associated with hypogonadism though rarely gynaecomastia[147]. The observed rise of serum prolactin in the three hypercapnic subjects in this study (table 10) does not seem to have been induced by pharmacological agents such as methyldopa, metoclopramide, or the phenothiazines that are known to have antidopaminergic actions[147]. Thus it is tempting to speculate

that the observed hyperprolactinaemia in these three individuals also arose as a result of hypoxia-induced interruption of the hypothalamic-pituitary axis.

Early morning urinary aldosterone values were higher in the hypercapnic group, and this might reflect the hyperaldosteronism known to occur with respiratory failure. Hyperaldosteronism might account in part for the fluid retention and reduction in total body potassium now known to occur in cor pulmonale[131].

In conclusion, though caloric intake values estimated from dietary histories must be viewed with caution, we have shown no evident alteration in calorie intake or absorption of food to account for changes in body habitus in COAD. There do appear to be profound changes in anabolic steroid output and possibly also in prolactin production, perhaps as a result of hypoxia affecting the hypothalamic-pituitary axis. We postulate that such alterations in hormone production might be causally related to the fairly pronounced and contrasting changes in body habitus found in the two distinct clinical patterns in patients with chronic bronchitis and emphysema.

CHAPTER VI

SERUM TESTOSTERONE DEPRESSION ASSOCIATED WITH HYPOXIA IN RESPIRATORY FAILURE[148]

This extended study of 37 COAD patients confirms a correlation between the level of hypoxia, but not the level of hypercapnia, and the degree of testosterone reduction. Eighty percent of these patients with a PaO_2 below 6.6kPa (50mmHg) and 43 percent above this but below 10kPa (75mmHg) have low serum testosterone levels.

INTRODUCTION

This study followed that of Chapter V in which amongst other findings we demonstrated low serum testosterone values in COAD subjects, particularly those who were "blue bloaters". The aim of the project was to extend the number of COAD patients and to confirm whether there is a correlation between arterial oxygen tension and serum testosterone value. This study is similar to that published[148] but numbers have now been extended from twenty-two to thirty-seven patients.

METHODS

Thirty-seven male patients with COAD were studied. In twenty-two of these the condition was stable and seven others were studied while in acute respiratory failure. A further eight were studied while in cor pulmonale failure and again when recovered and stable some months later. Thus fifteen assessments were made on acutely ill patients and thirty when stable. Criteria for the presence of COAD and techniques for measurement of arterial blood gases and serum testosterone were as previously described (Chapter I). The correlation between serum testosterone and arterial blood gas tensions was tested by a least sum of squares linear fit.

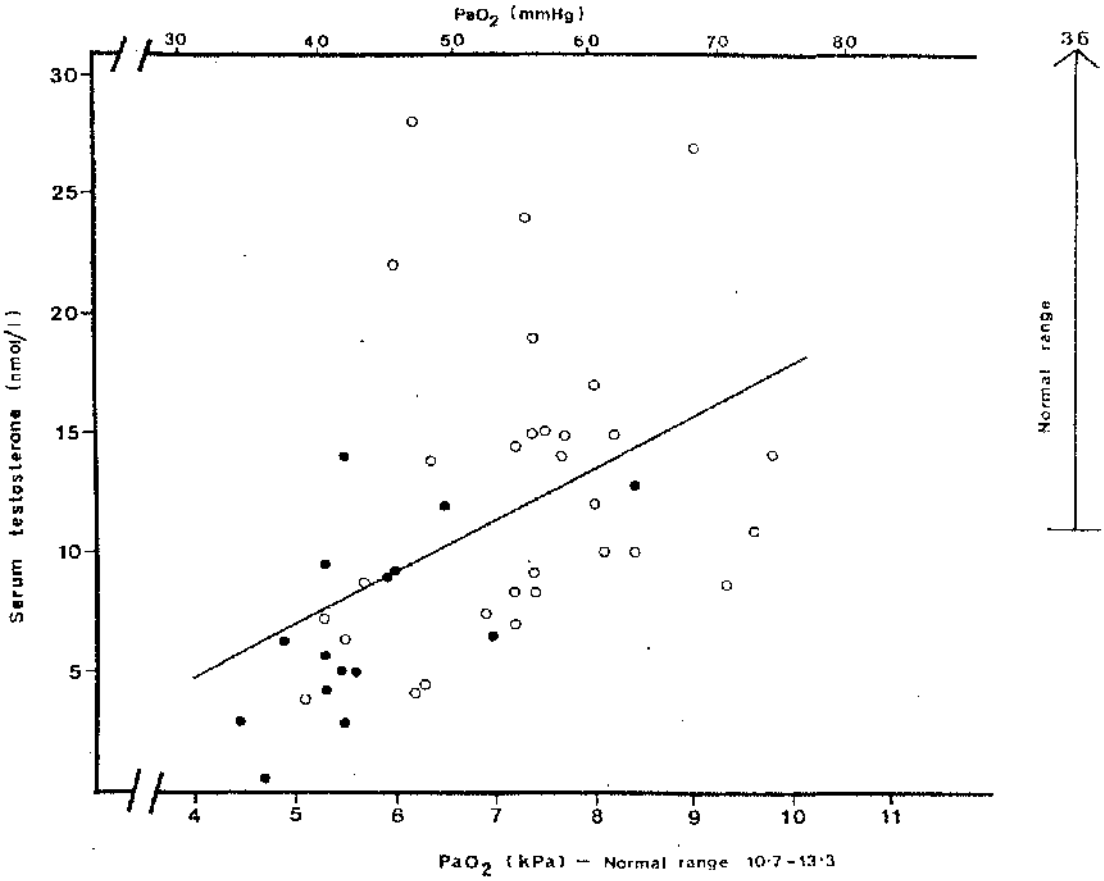
RESULTS

All patients had hypoxia of greater or lesser degree (figure 8) and most were hypercapnic (figure 9). In twenty-six of the forty-five determinations serum testosterone levels were frankly low and in the majority of the remainder values were towards the lower limit of the normal range. There was a correlation between the degree of hypoxia and the degree of testosterone reduction ($p<0.01$) but not between degree of hypercapnia and degree of testosterone reduction.

DISCUSSION

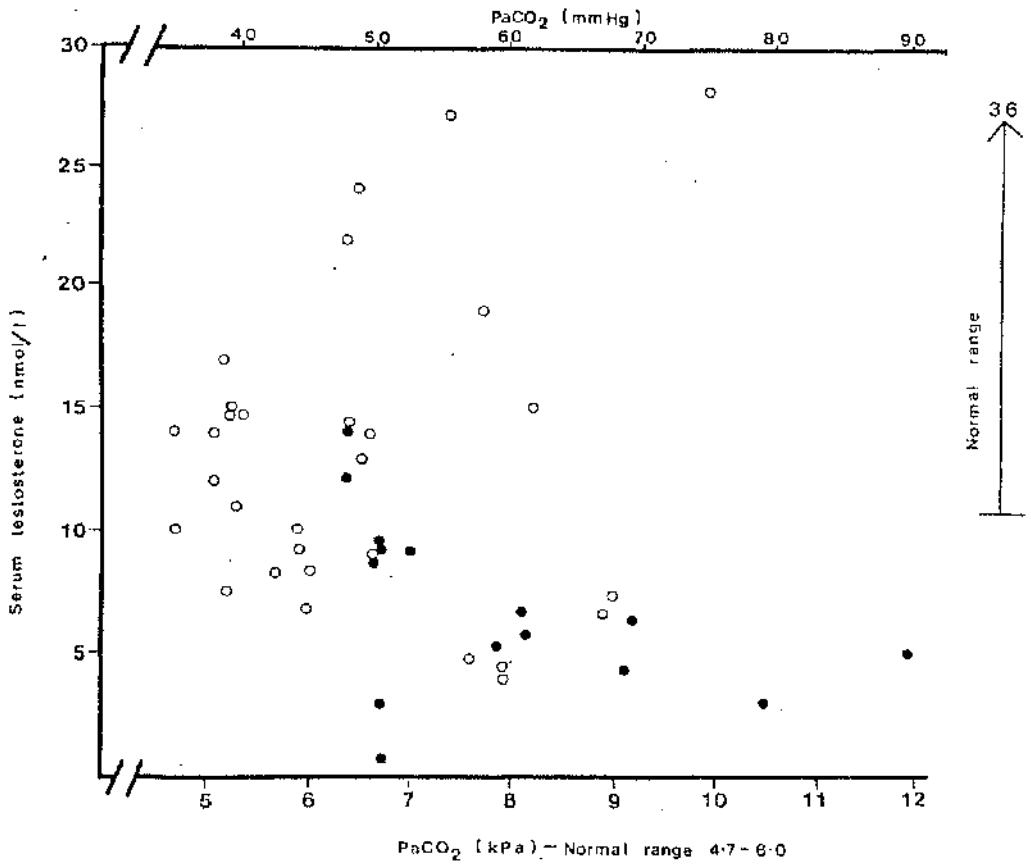
This extended study confirmed our earlier impression that the reduction in serum testosterone in COAD appears to be a function of hypoxia. Though in the initial study there was also a correlation between the degree of hypercapnia and reduced testosterone this was not the case in this study. However the relationship between hypercapnia and testosterone only just fails to reach significance and if the "rogue point" ($PaCO_2$ 10kPa; serum testosterone 28mmol/l) is excluded then there is indeed a significant correlation ($p<0.01$). We have noted some COAD individuals with hypoxia and normocapnia to have low serum testosterone and feel that hypercapnia and low serum testosterone are not causally related, the association probably being an indirect one, the more hypoxic COAD patients tending to have higher $PaCO_2$ levels.

Presuming the sample of thirty-seven patients is typical of the condition it would appear from figure 8 that in COAD patients with a PaO_2 below 6.6kPa (50mmHg) approximately 80 percent have low serum testosterone values. Even in those subjects with PaO_2 values between 6.6kPa (50mmHg) and 10kPa (75mmHg) 43 percent had



Correlation between arterial oxygen tension and serum testosterone in 30 stable COAD male patients (○) and in 15 with respiratory failure (●). Significance $r = 0{\cdot}473$, $p < 0{\cdot}01$.

FIGURE 8



Correlation between arterial carbon dioxide tension and serum testosterone in 30 stable COAD male patients (○) and in 15 with respiratory failure (●), r = -0·220, p = not significant.

FIGURE 9

low serum testosterone levels and we contend that in view of the fact that chronic bronchitis and emphysema are very common conditions they probably represent the commonest cause of this abnormal endocrine state. It seems remarkable indeed that this association has not been described previously.

CHAPTER VII

HYPOTHALAMIC-PITUITARY DYSFUNCTION IN RESPIRATORY HYPOXIA[149,150]

Combined pituitary stimulation tests indicate suppression of the H-P-Testicular axis while other aspects of hypothalamic and pituitary function remain comparatively well preserved. The most consistent hormone abnormalities apart from low testosterone are those observed for the gonadotrophins. Low basal levels of LH and FSH point to a hypothalamic or pituitary rather than a testicular fault. Normal LH response to injected GnRH tends to suggest the pituitary is coping normally and that the hypothalamus is responsible for the deficient steroidogenesis.

INTRODUCTION

Having established that serum testosterone is low in hypoxic COAD sufferers the next step was to determine whether the hypothalamus, pituitary or testis itself was suppressed in this situation. In figure 10 the hypothalamo-pituitary-testicular axis in man is shown. Normally the hypothalamus secretes gonadotrophin releasing hormone (GnRH) which in turn stimulates the anterior pituitary to secrete luteinising hormone (LH) and follicle stimulating hormone (FSH). LH then stimulates the Leydig cells of the testis to secrete testosterone and FSH the Sertoli cells to produce spermatozoa. Testosterone by feedback inhibits LH production by the anterior pituitary and perhaps also GnRH by the hypothalamus.

In end organ failure or suppression which is seen in the male eunuch and in Klinefelter's syndrome low testosterone is associated with high LH levels as there is no negative feedback by testosterone. Where pituitary failure is responsible for low testosterone output, LH levels are low or normal and are not stimulated by injected GnRH. Where low testosterone secretion is caused by hypothalamic dysfunction, LH levels are low or normal but LH secretion by the pituitary is

The Hypothalamic-Pituitary-Testicular Axis: Adult Man

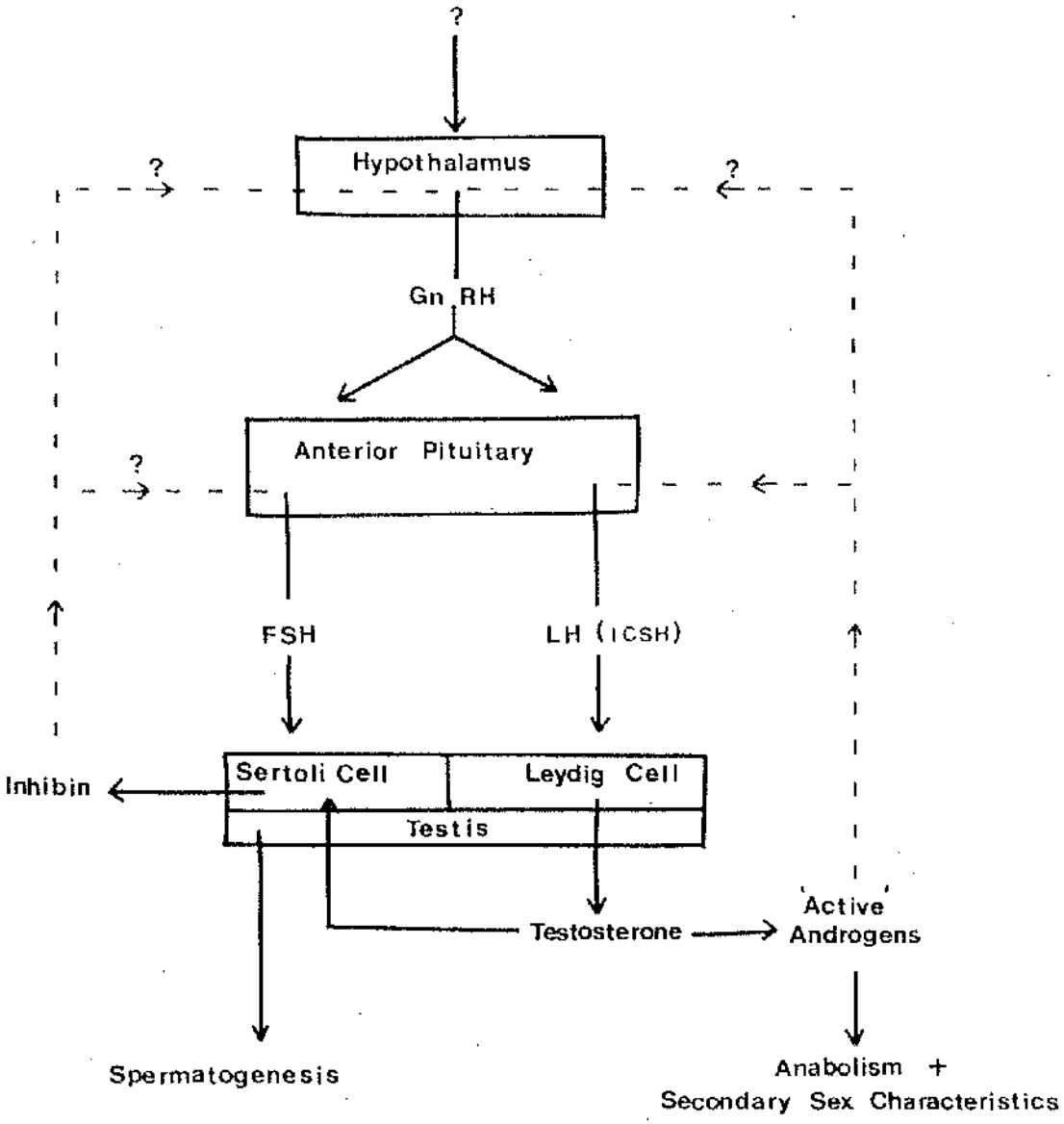


FIGURE 10

stimulated by injected GnRH as the pituitary itself is normal.

Our initial study (Chapter V)[139] demonstrated that in hypoxic COAD subjects with low serum testosterone LH levels were not elevated suggesting either hypothalamic or pituitary suppression. This project sets out to elucidate the site of the lesion and also to determine prolactin status, the integrity of the hypothalamo-pituitary-thyroid axis and human growth hormone (HGH) and cortisol status.

METHODS

Eight stable male chest clinic patients were chosen. Investigations in common with previous projects were performed as previously described. Within two weeks of the baseline investigations patients attended a metabolic unit having fasted overnight. Each then had a combined pituitary stress test as described in Chapter I. Basal prolactin and T_3 and T_4 were measured.

Our laboratory normal data for all these methods have been obtained from appropriate volunteer and hospital inpatient populations. For this study in particular the LH and FSH levels observed in hypoxic men after the administration of GnRH were compared with data obtained from eight age-matched control male subjects. Statistical comparisons were made using Wilcoxon's Rank test.

RESULTS

Objective evidence of COAD in all subjects is presented in table 11 together with a record of the drugs prescribed at the time of study. The basal prolactin and thyroid function test results are recorded in table 12 together with data relating to the TSH response to TRH and the HGH and cortisol responses to insulin-induced

Hypothalamic-pituitary function study - Subjects studied, indices of chronic obstructive airways disease and drug histories

Subject	Age (yr)	FEV_1 (% predicted)	FEV_1/FVC (%)	PaO_2 (kPa)	$PaCO_2$ (kPa)	Drugs prescribed
1	36	27	57	7.7	7.7	Spironolactone, frusemide, theophylline
2	47	61	52	10.0	5.4	Salbutamol
3	50	27	60	5.7	6.6	Spironolactone, frusemide
4	50	16	50	6.4	7.8	Spironolactone
5	52	53	59	8.4	6.5	Frusemide K, theophylline, allopurinol
6	53	26	37	9.3	6.6	Spironolactone, frusemide, theophylline
7	57	25	62	5.3	8.1	Frusemide K
8	60	36	47	6.5	5.7	Salbutamol, frusemide K, allopurinol, digoxin
Normal values		100	70-90	10.7-13.3	4.7-6.0	

Table 11

Anterior pituitary function in men with chronic obstructive airways disease. Basal prolactin status and thyroid function and responses of TSH to TRH and HGH and cortisol to insulin-induced hypoglycaemia

Subject	Basal serum prolactin (mU/l)	Basal serum T_4 (nmol/l)	Basal serum T_3 (nmol/l)	Serum TSH responses (mU/l)			Minimum plasma glucose (mmol/l)	Serum HGH peak response (mU/l)	Serum cortisol maximum increment (nmol/l)
				0'	30'	60'			
1	272	84	1.9	3.0	9.8	6.8	0.8	42	75
2	168	99	0.9	1.9	10.0	9.1	1.1	37	450
3	200	116	2.5	2.2	7.7	7.0	1.1	57	200
4	187	75	1.5	1.8	6.6	6.4	0.9	33	215
5	130	76	2.4	4.3	6.1	7.9	1.8	21	340
6	256	110	2.2	4.7	11.0	8.1	0.9	40	525
7	124	96	2.4	2.7	6.6	4.4	1.1	32	570
8	271	63	1.8	3.7	5.7	6.5	0.5	21	200
Normal values	60-360	55-144	0.9-2.8	UD-8.0	Increment >3.6 30'>60'		<2.2	>15	>200

UD = Undetectable

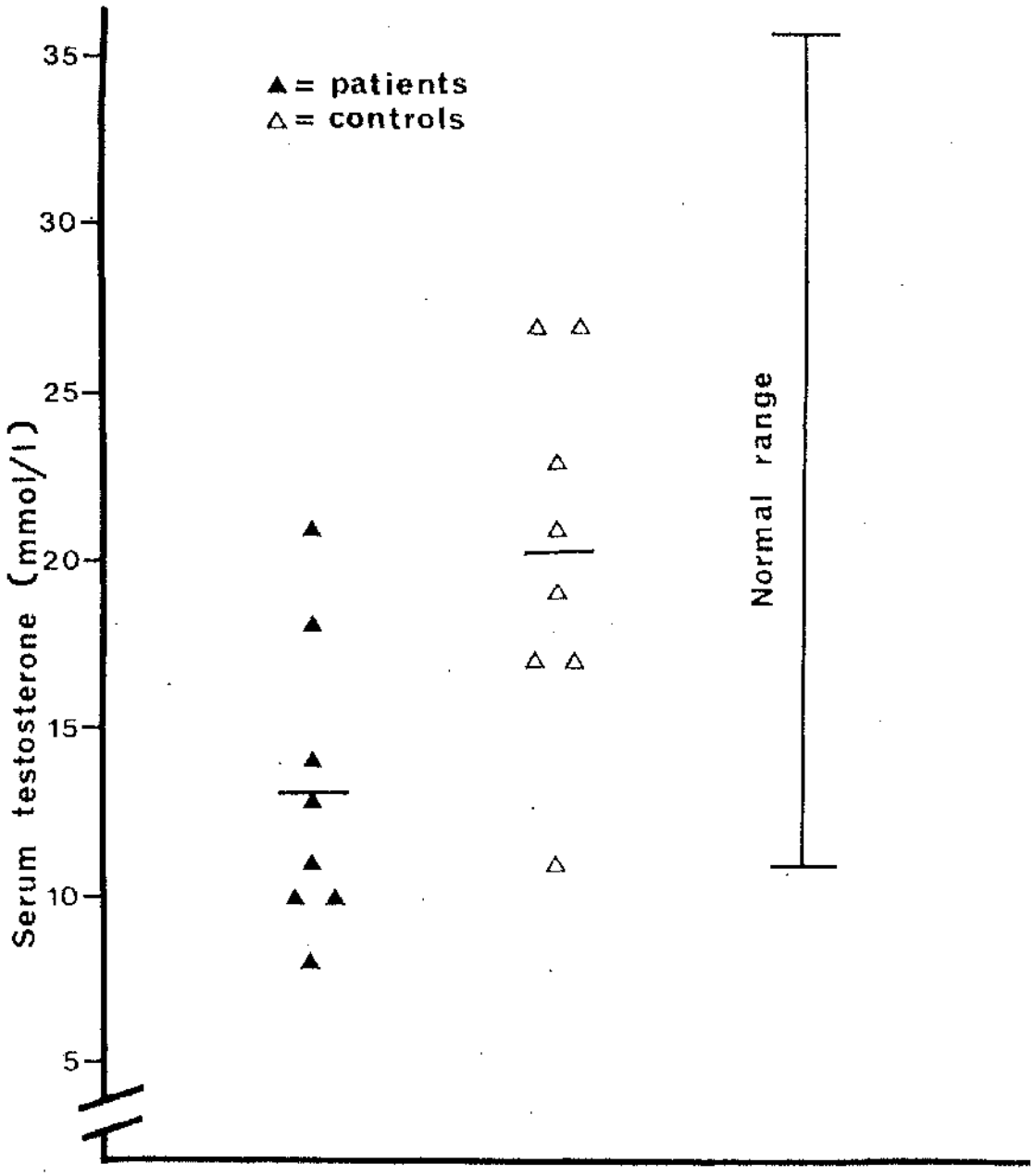
Table 12

hypoglycaemia. All subjects had normal prolactin levels and were biochemically euthyroid at the time of study. An adequate increment of serum TSH occurred in six cases but in subjects 5 and 8 the peak TSH level was low and was observed at 60 minutes rather than 30 minutes after TRH. All subjects achieved adequate hypoglycaemia after 0.2 units/kg of insulin, and in all cases the peak serum HGH level exceeded the lower limit of normal. Four of the eight subjects had adequate cortisol responses to hypoglycaemia, three had equivocal responses (subjects 3,4 and 8) and one (subject 1) had a clearly subnormal response.

Basal levels of serum testosterone ($p<0.05$) (figure 11), LH ($p<0.02$) (figure 12) and FSH ($p<0.01$) (figure 13) were significantly lower in patients than in age-matched controls. A normal pituitary response of LH was noted after GnRH administration to patients (figure 12) but the FSH response was significantly lower than in the control group both at 30 minutes and 60 minutes after stimulation (figure 13).

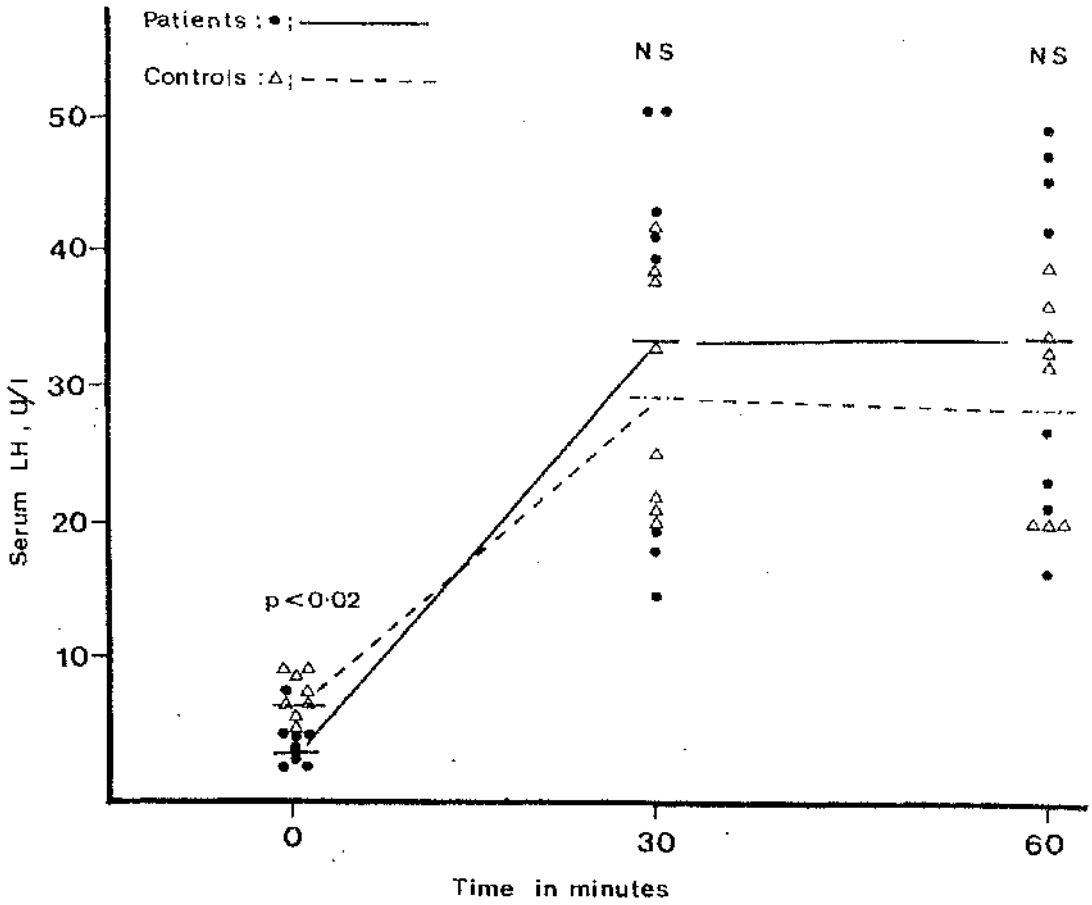
DISCUSSION

This study confirmed our previous finding of low serum testosterone levels in hypoxic men with COAD. We have shown that hormone binding globulin capacity is not reduced in these hypoxic subjects (unpublished data) and therefore these subnormal testosterone levels are real and will be accompanied by a fall in the circulating level of free androgen. Low levels of testosterone have also been reported in chronic liver disease[151] but we are confident that liver disease was not a causative factor in our study since none of our cases had liver congestion from cor pulmonale and all had normal biochemical indices of liver function.



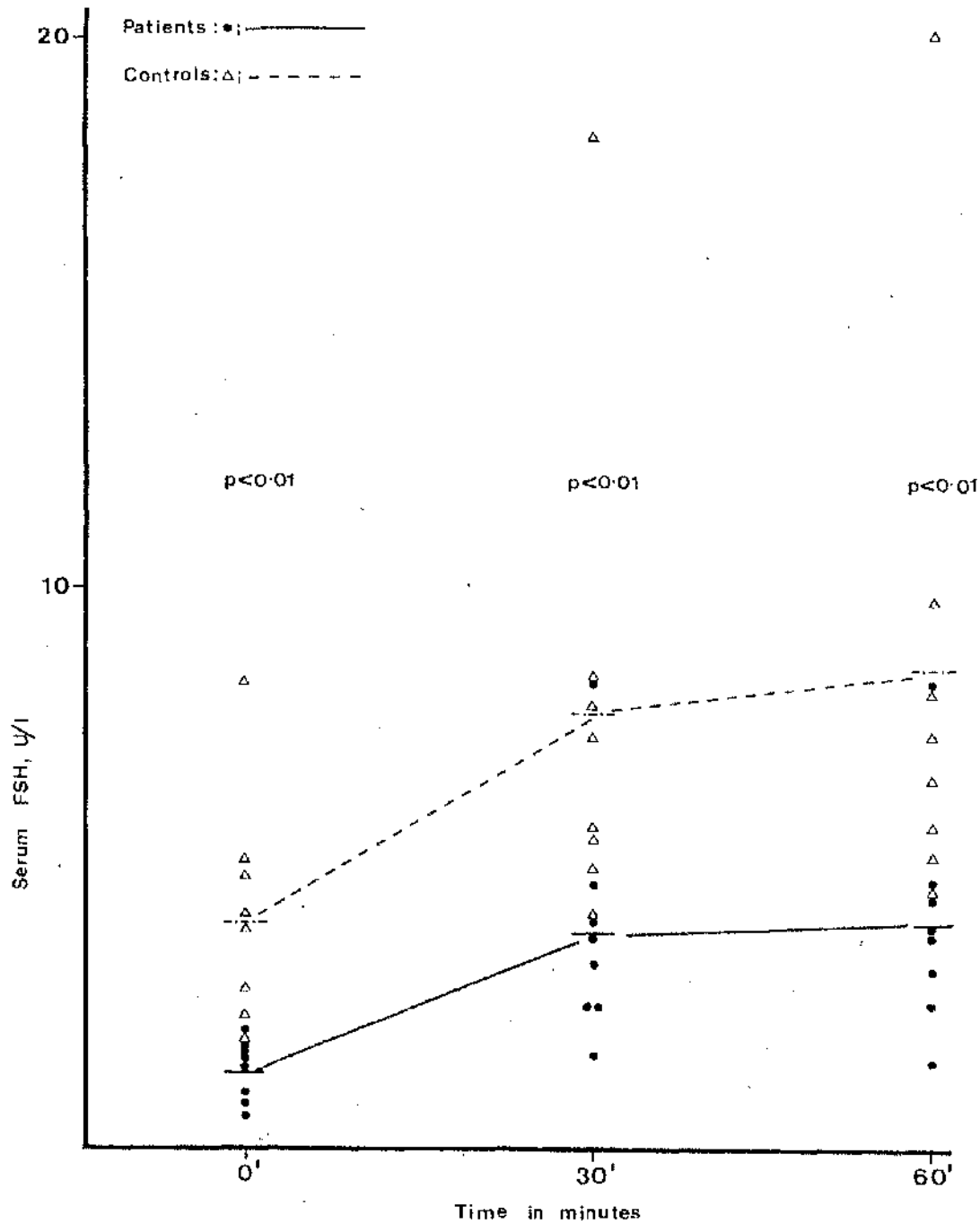
Serum testosterone in eight stable COAD subjects and in eight age matched controls ; Significance of difference , $p < 0{\cdot}05$

FIGURE 11



Basal serum LH and LH response to injected GnRH in eight male COAD patients and controls

FIGURE 12



Basal serum FSH and FSH response to injected GnRH in eight male COAD patients and controls

FIGURE 13

The extent of testosterone deficiency is less marked in this study than in our previous series of COAD subjects who were in relapse and more hypoxic when tested.

Basal serum prolactin values were all normal in this series of patients although we have previously noted high levels in three of 16 COAD subjects[139]. This study suggests that elevated prolactin is seen only occasionally in COAD and is not closely related to the low testosterone levels.

Basal thyroid hormone levels were normal in the subjects studied confirming our previous results[139] and as expected there was a normal increment of TSH in most subjects after a bolus injection of TRH. The delayed response of TSH in two subjects (table 12) is of interest since this pattern has been linked with hypothalamic dysfunction[18]. However, our two isolated observations indicate that at most hypoxia causes a very minor change in the hypothalamo-pituitary-thyroid axis.

Insulin-induced hypoglycaemia stress in normal subjects promotes secretion of HGH and ACTH (thence cortisol) from the anterior pituitary and is a test therefore of anterior hypophyseal function. Hypoglycaemia resulted in a normal HGH response in all subjects, so hypoxia would appear to have no effect on the synthesis and secretion of this hormone. No consistent effect of hypoxia could be shown on the cortisol response to hypoglycaemia there being four normal responses and four equivocal or abnormal. However, with the exception of subject number 8 (equivocal response), the latter group were receiving spironolactone, the metabolites of which are known to cross-react in the assay system used (GH Beastall, unpublished data), so it would be unwise to interpret these results as indicating adrenal insufficiency. Moreover we would not expect

the hypothalamo-pituitary-adrenal axis to be suppressed by hypoxia since there is an increase in serum cortisol in healthy people exercising in conditions of hypoxia compared to normoxia[152], corticosteroid output is increased in hypoxia of altitude[97-101] and the H-P-Adrenal axis has been found to be normal in COAD by other workers[93].

The only consistent abnormalities of pituitary hormone homeostasis were those observed for the gonadotrophins. Significantly low basal levels of both FSH and LH compared with age-matched controls would seem to exclude primary testicular failure as a cause of the low serum testosterone of COAD and to suggest instead either a hypothalamic or pituitary lesion. The normal LH response demonstrates that the pituitary can be stimulated by exogenous GnRH in these subjects and so provides evidence in favour of a hypothalamic cause of the deficient steroidogenesis.

Theoretical evidence can be advanced in favour of such hypothalamic involvement. It is known that the normal secretion of LH relies upon a precisely timed pulsatile release of GnRH[153] which if upset by hypoxia could lead to subnormal LH and testosterone concentrations. Alternatively such a disruption of GnRH rhythm might be brought about by raised intracranial pressure which occurs in hypercapnia and which has been implicated as the cause of hypothalamic hypopituitarism in patients suffering from "normal-pressure" hydrocephalus[154].

The observation of a reduced FSH response to GnRH in COAD patients in the presence of a normal LH response is of great interest as it would appear to imply a pituitary lesion inconsistent with the theories outlined in the previous paragraph.

However, it is well established that the feedback control of LH by testosterone and its metabolites differs appreciably from that of FSH. Indeed androgens appear to have opposite effects on LH and FSH secretion since pretreatment of pituitary cells with androgen can markedly inhibit the LH response to GnRH while the effect of FSH is stimulatory[155]. If the corollary applies then the pattern of gonadotrophin responses observed in this study might be more easily explained. The observed fall in serum testosterone could affect the pituitary directly and lead to a diminution in FSH response but not the LH response to exogenous GnRH. The theory would gain support should the FSH response to GnRH in affected patients return to normal as the serum testosterone rises after reversal of hypoxia or with testosterone replacement therapy.

It seems then that abnormalities of hypothalamo-pituitary function in COAD are primarily located in the hypothalamo-pituitary-testicular axis though minor abnormalities may also occur in the H-P-Thyroid and H-P-Adrenal axes.

CHAPTER VIII

ENDOCRINE STUDIES IN ACUTE COR PULMONALE AND AFTER RECOVERY[156,157]

Serum concentrations of testosterone, FSH, LH and DHAS rose during recovery from a severe exacerbation of cor pulmonale in COAD, apparently confirming that hypoxia suppresses the hypothalamus and/or pituitary and that such suppression is reversible.

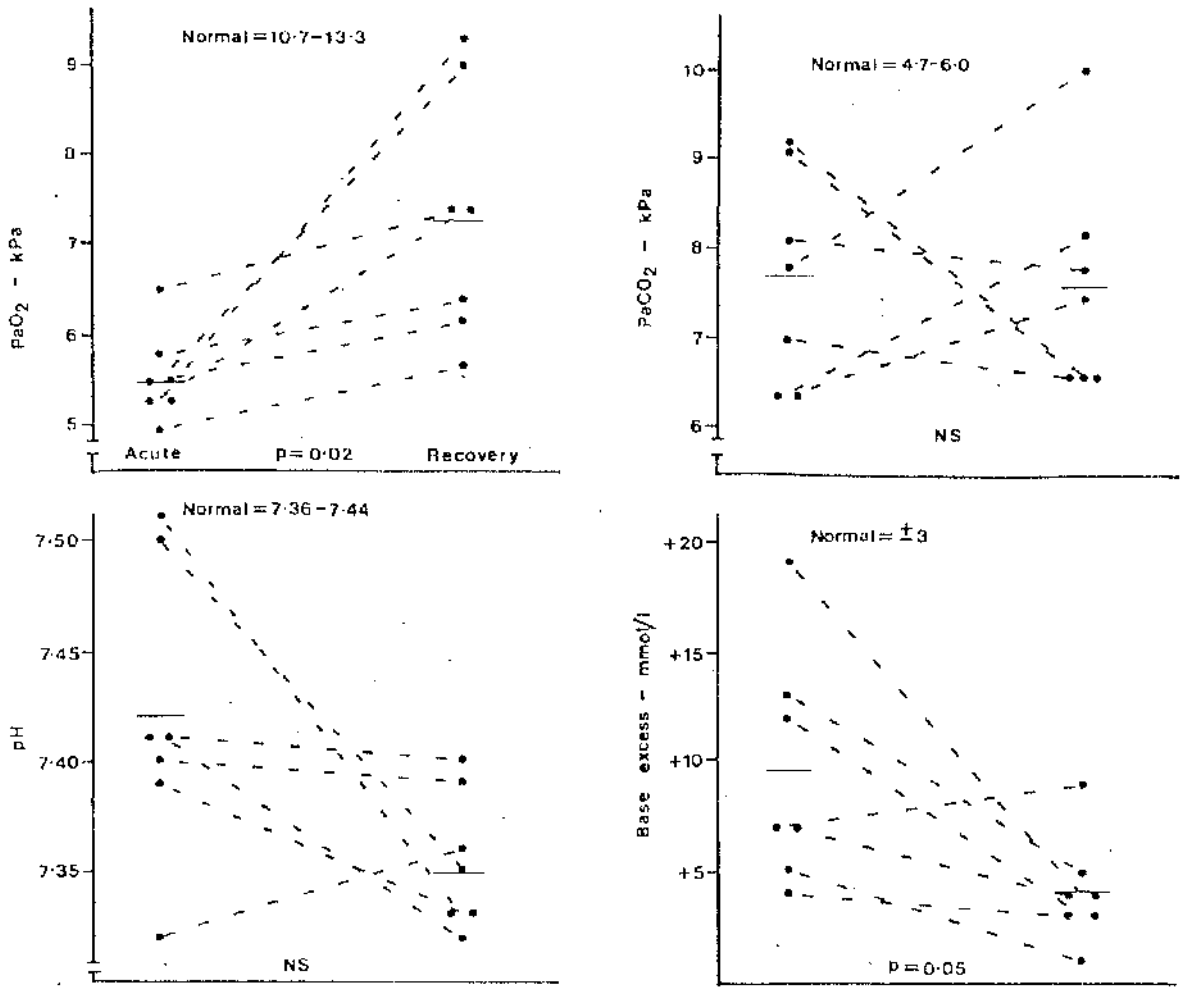
INTRODUCTION

Our earlier studies having confirmed that the hypothalamo-pituitary-testicular axis is suppressed in hypoxic chronic obstructive airways disease with resultant low serum testosterone, it seemed logical then to assess endocrine function of acutely ill COAD patients with severe hypoxia and to repeat the investigations after recovery to determine whether endocrine function fluctuates with changes in severity of hypoxia. It was decided to concentrate on the H-P-Testicular axis in view of the fact that thyroid and adrenal function had been shown to be relatively normal in stable COAD subjects[139,149] but to assess other androgens in addition to testosterone and also prolactin status.

METHODS

Seven men (age range 36-63) admitted in cor pulmonale failure were studied. All had chronic bronchitis as previously defined and had had grade 3 or 4 dyspnoea[133] for several years. Patients with additional unrelated disease were excluded. All had peripheral oedema and raised jugular venous pressures on admission and were hypoxic and hypercapnic (figure 14). Standard treatment was with oxygen, antibiotics, diuretics, bronchodilators and physiotherapy.

Investigations were started three or four days after admission



Arterial blood gas values in seven patients in acute cor pulmonale and after recovery

FIGURE 14

when oedema had largely subsided and patients were sufficiently well to be studied. In this and in subsequent studies dehydroepiandrosterone sulphate (DHAS) rather than dehydroepiandrosterone (DHA) was assayed as this had been found to be a more stable compound. Blood for hormone measurements was taken at 1100 hours. Arterial blood gas and serum levels of all hormones were assessed as previously described (Chapter I). Statistics were applied using the Wilcoxon test for paired differences.

After recovery some months later all investigations were repeated.

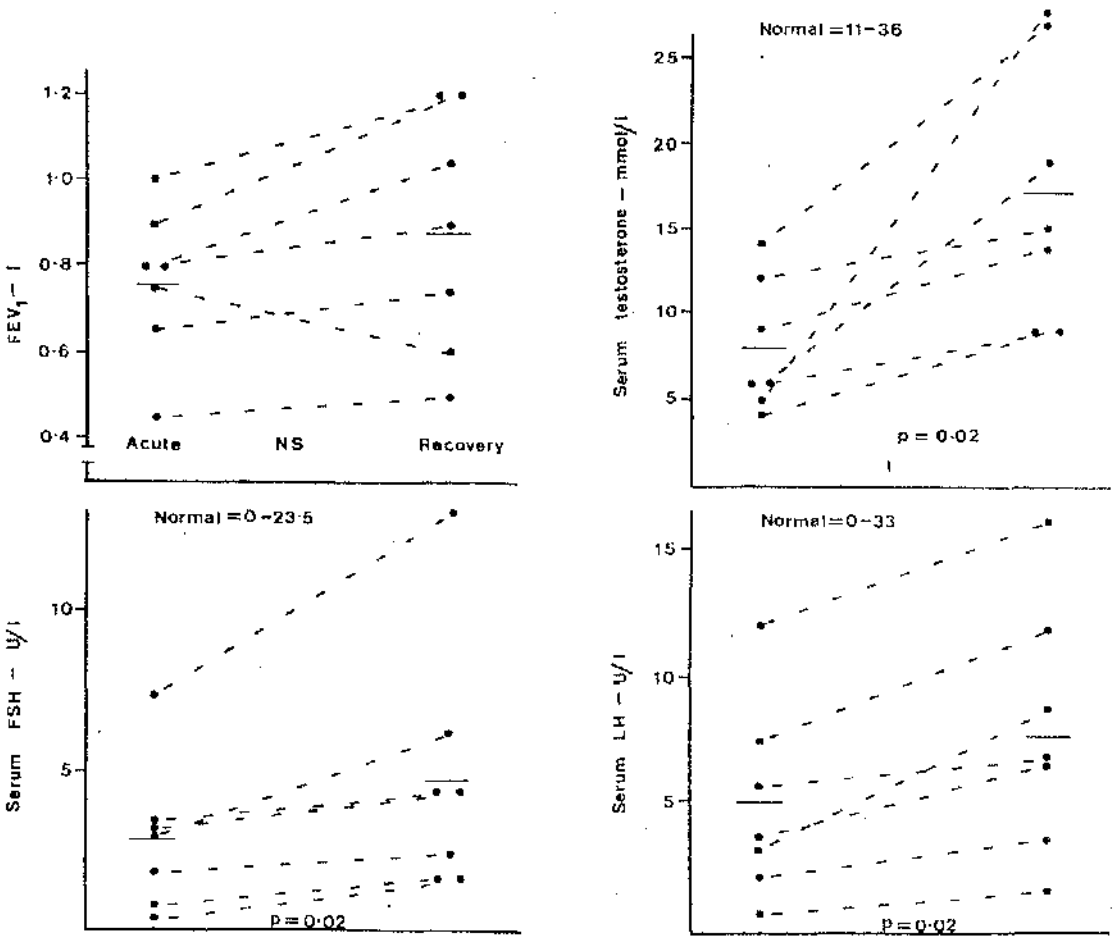
RESULTS

Initially all patients had grade 4 dyspnoea and five of the seven had improved to grade 3 during the recovery study period. There was however no significant increase in FEV_1 with recovery (figure 15) though PaO_2 improved in all patients ($p=0.02$) (figure 14). There was no consistent change in $PaCO_2$. Arterial blood pH and base excess fell in six of the seven patients on recovery.

Serum testosterone, FSH and LH rose significantly (figure 15) when clinical recovery took place ($p=0.02$). Both FSH and LH levels normally fluctuate but the rise accompanying clinical improvement, together with our earlier finding of low follicle-stimulating hormone and luteinising hormone in chronic obstructive airways disease compared with controls[149], confirms that these hormones are indeed further suppressed in the acutely hypoxic state. Serum dehydroepiandrosterone sulphate and urinary 17-ketosteroids also rose significantly ($p<0.05$) though serum androstenedione and prolactin did not (figure 16).

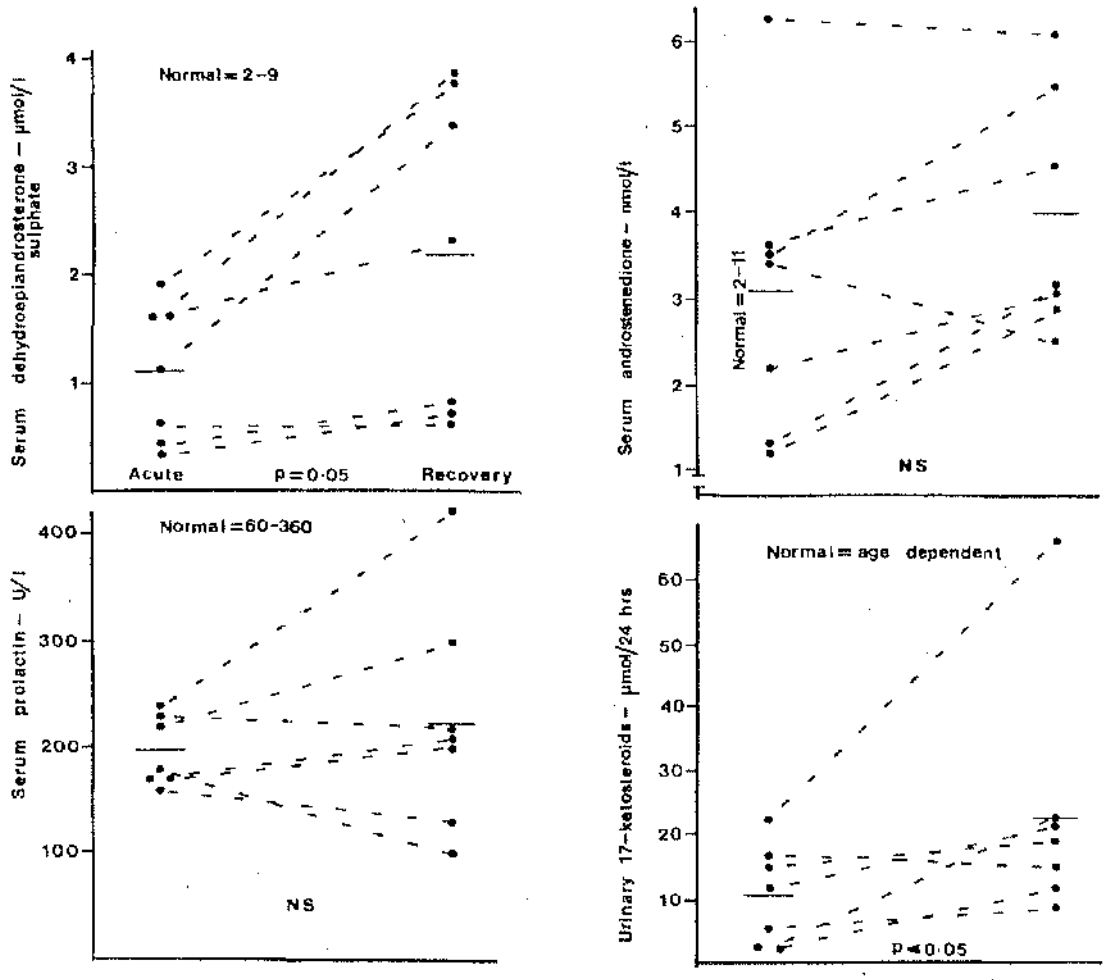
DISCUSSION

From this study we can conclude that integrity of the



Forced expiratory volume in one second, serum testosterone and serum FSH and LH in acute cor pulmonale and after recovery.

FIGURE 15



Serum hormones and urinary 17–ketosteroids in acute cor pulmonale and after recovery

FIGURE 16

hypothalamo-pituitary-testicular axis is compromised during severe hypoxia but recovers somewhat with improved oxygenation. The increase in urinary 17-ketosteroids, which are largely androgen metabolites, reflects increased testosterone production with recovery. The rise in the adrenal androgen dehydroepiandrosterone sulphate from frankly low to normal levels in four cases and lesser increase in androstenedione, which is partly adrenal and partly testicular in origin, suggests that hypoxia may also influence their production, perhaps at the hypothalamic level.

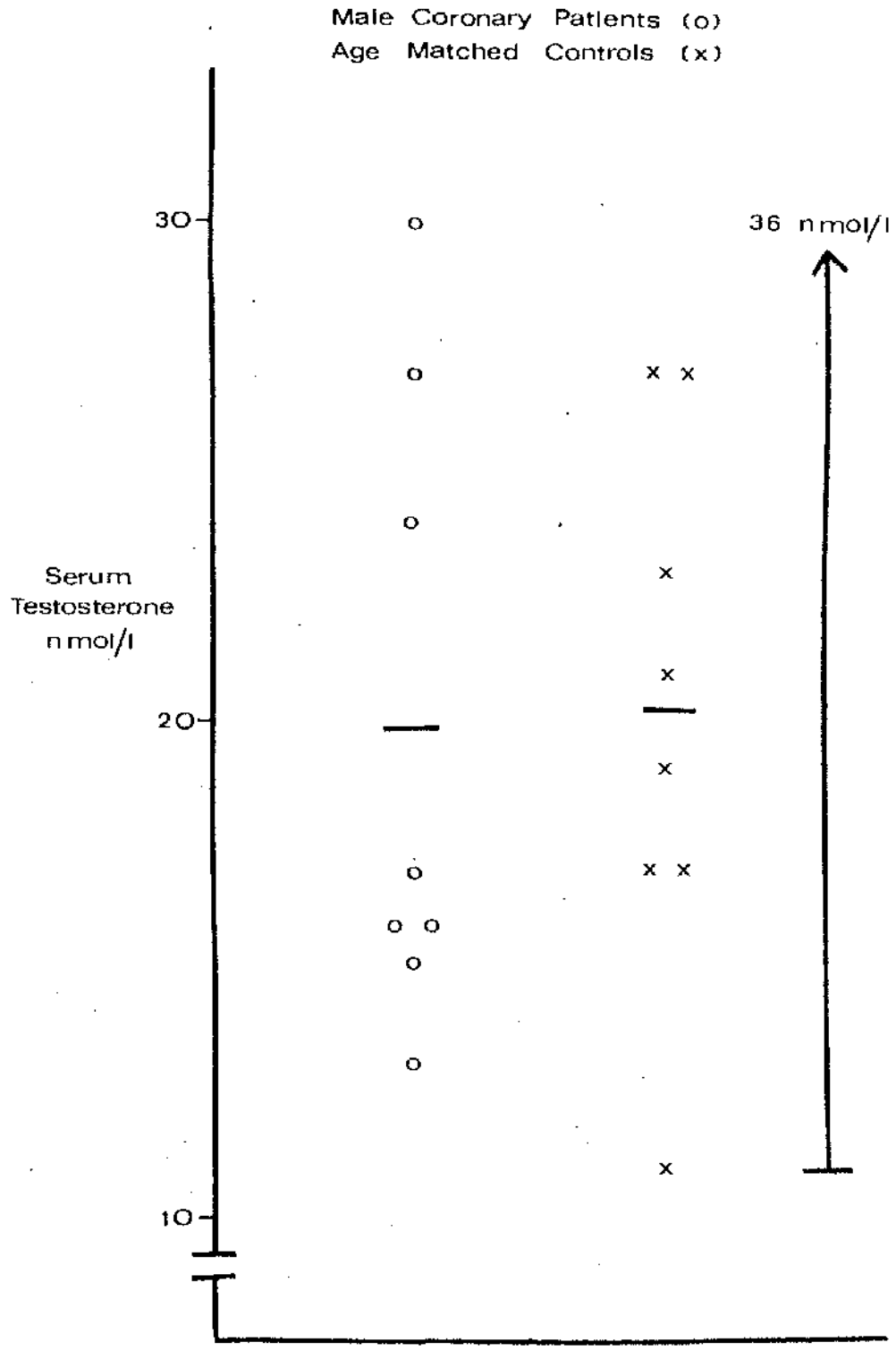
Though we assume hypoxia to be the suppressing influence, theoretically other indices of blood gas status could influence the hypothalamus or pituitary. Unlike PaO_2, $PaCO_2$ values did not change consistently with recovery. Moreover mean $PaCO_2$ value remained similar with recovery. These findings along with our earlier observation of individual hypoxic but normocapnic subjects with low serum testosterone levels suggest that $PaCO_2$ is not the suppressing factor. Though arterial pH tended to fall with recovery levels were within or near the normal range (7.36-7.44) and it seems unlikely therefore that pH is a factor. Bicarbonate status (base excess) did significantly alter with recovery. High base excess values in the acute stage reflected a metabolic alkalosis compensating for the respiratory acidosis. Conceivably such changes could influence the H-P-T axis but this is not a recognised feature in other abnormalities of acid-base status.

An alternative mechanism for H-P-T suppression in this situation is stress of emergency admission to hospital in some way affecting the hypothalamus. This seems unlikely in view of the fact that we have noted H-P-T dysfunction in stable outpatients[149]. However to exclude this possibility we have looked at serum testosterone in

eight men admitted as emergencies with myocardial infarction and have found values to be normal as compared with age-matched controls (figure 17).

Heavy cigarette smoking has been shown to reduce serum testosterone by about 20 per cent and this is reversed by stopping smoking[158]. However the low testosterone values in this study are not related to smoking as values are much lower than could be explained by smoking alone and because some non and ex-smokers in our studies have had very low values.

Prolactin values were normal even in the acute stage and remained unaltered which suggests our impression that levels are only occasionally elevated in COAD is correct.



Serum testosterone in eight men with acute myocardial infarction & controls. No significant difference.

FIGURE 17

CHAPTER IX

SEX HORMONE SUPPRESSION IN HYPOXIC PULMONARY FIBROSIS[159,160]

Hormone changes in restrictive lung disease are essentially similar to those of COAD. Serum testosterone again tends to be low in proportion to the level of hypoxia. As hypercapnia does not occur in this condition it need no longer be considered in the aetiology of hormone suppression.

INTRODUCTION

Having established that the hypothalamo-pituitary-testicular axis is suppressed in hypoxic chronic obstructive airways disease patients the next step was to establish whether the same was true of hypoxic restrictive lung disease (RLD). If the theory that hypoxia is the suppressing influence is true it seems likely that such patients would have similar endocrine disturbance. Accordingly therefore we set out to study patients with pulmonary fibrosis assessing the H-P-T axis but also thyroid and prolactin status.

METHODS

Eight men attending a chest clinic and considered to have radiographic evidence of pulmonary fibrosis were chosen. All had fine late inspiratory crackles and in no case was an aetiological factor incriminated. Severity of breathlessness was gauged using the Medical Research Council Questionnaire on Respiratory Symptoms[133]. Lung function studies included FEV_1, FVC, total lung capacity (TLC) and measurement of single breath transfer factor (TF). Values were compared with predicted normal[14,15]. Arterial blood gases were assessed as previously described. Patients found to have carbon dioxide retention ($PaCO_2$>6.0kPa:45mmHg) were excluded.

Within one week of the above baseline investigations the patients had pituitary function assessed each at approximately the same time of day (10.30am-12midday).

RESULTS

Objective evidence of pulmonary fibrosis is presented in table 13. In all cases FEV_1/FVC ratio was 70% or greater excluding significant airways obstruction. All patients had both TLC and TF of less than 80% of predicted normal value in keeping with a restrictive defect. In addition all subjects were hypoxic and normocapnic. Subjects 2 and 8 were each studied a second time several months later (Nos 2b and 8b) when clinical deterioration accompanied by a drop in PaO_2 had occurred. Subject 2 was not sufficiently well to have TLC and TF measured on repeat testing. It can be seen that dyspnoea at rest (grade 4) was present in most of the patients and that the only one with minimal dyspnoea (No 7) was the patient with the highest PaO_2.

Two subjects (Nos 1 and 4) had frankly subnormal serum testosterone levels while the values for two others (Nos 2 and 8) became subnormal (2b and 8b) with clinical deterioration (table 14). There was a significant correlation ($p<0.05$) between serum testosterone and PaO_2 (figure 18). Sex hormone binding globulin (SHBG) values were slightly elevated in four of the six patients in whom it was measured. Serum LH and FSH response to injected GnRH was not performed in subject 1. Of the others three subjects (Nos 2b, 3 and 4) had subnormal LH responses, two of these (Nos 3 and 4) having subnormal FSH responses also. Initial high basal LH was noted in subjects 5 and 6 and high basal FSH in subject 5. Normal serum T_3 and T_4 values were obtained in all subjects (table 15) there being rather flat TSH response curves to injected TRH in subjects 7 and 8a.

Details of pulmonary function and arterial blood gases in eight male patients with pulmonary fibrosis

Patient	Age (yr)	FEV_1 (% predicted)	FEV_1/FVC (%)	TLC (% predicted)	TF (% predicted)	PaO_2 (kPa)	$PaCO_2$ (kPa)	pH	Base excess (mmol/l)	Grade of dyspnoea
1	35	39	83	40	20	6.1	4.7	7.41	-3	4
2a	45	47	70	79	19	8.3	4.1	7.45	0	3
b	"	30	84	-	-	6.1	4.3	7.50	-1	4
3	59	68	82	56	74	9.9	4.5	7.37	-2	3
4	72	90	73	78	29	7.2	4.4	7.47	+1	4
5	50	34	92	39	49	7.6	3.8	7.46	-1	4
6	41	61	73	69	67	10.1	5.2	7.38	-1	4
7	53	83	83	66	67	10.3	6.0	7.40	+3	1
8a	56	44	72	43	56	7.7	4.8	7.39	-2	4
b	"	44	80	44	44	4.4	4.3	7.47	+1	4
Normal values		100	70-90	100	100	10.7-13.3	4.7-6.0	7.36-7.44	±3	0

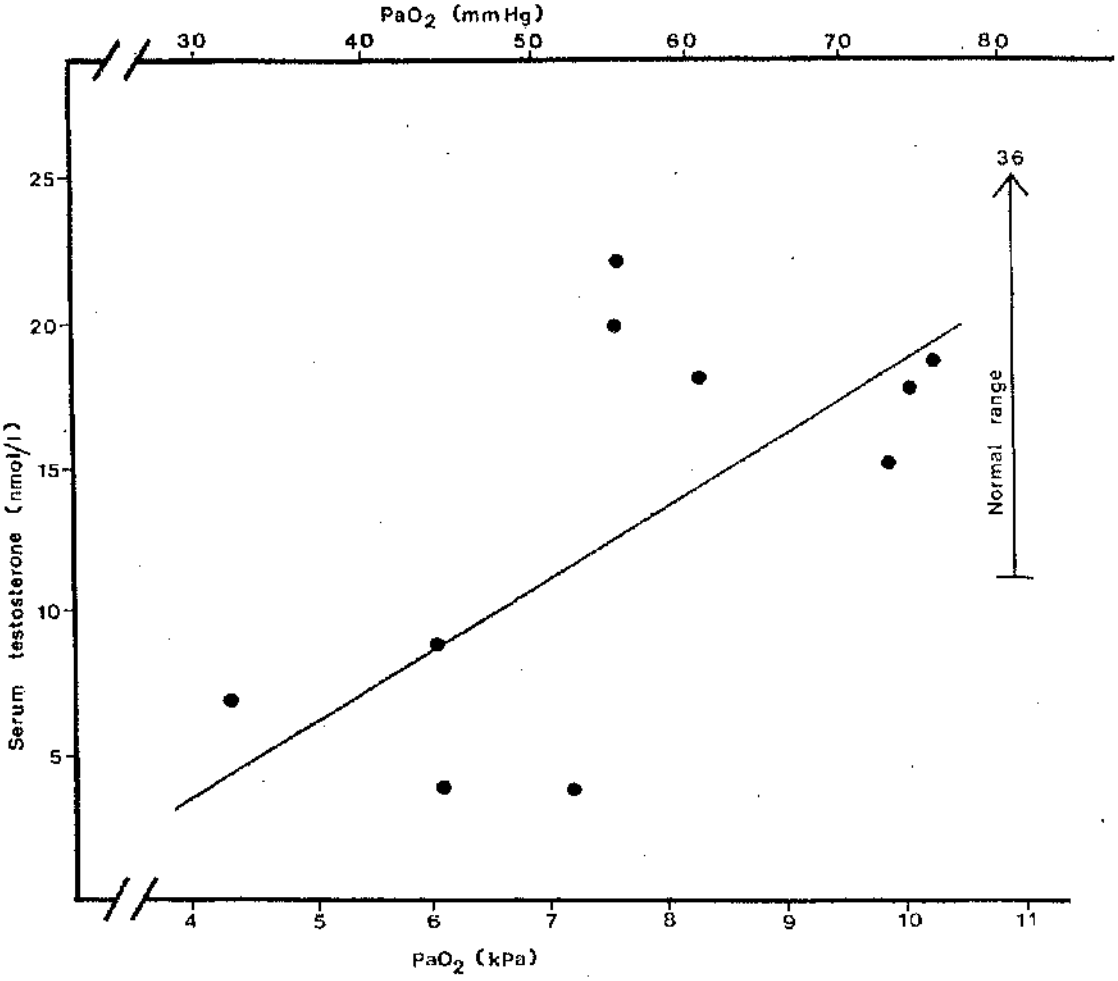
2a, 2b and 8a, 8b = Patients studied on two separate occasions.

Table 13

Anterior pituitary function in men with hypoxic pulmonary fibrosis. Basal testosterone values and gonadotrophin concentrations after GnRH injection

Patient	Serum 17 OHA (testosterone) (nmol/l) 0'	SHBG (nmol/l) 0'	Serum LH response (U/l)			Serum FSH response (U/l)		
			0'	30'	60'	0'	30'	60'
1	9.0	-	6.6	-	-	2.7	-	-
2a	18	-	5.2	>30	27	4.5	25	24
b	4.0	13	3.0	12	11	4.9	17	15
3	15	46	4.5	14	17	2.4	3.4	3.4
4	4.0	18	6.9	12	11	3.1	4.2	4.3
5	20	55	20	>100	>100	20	>30	>30
6	18	-	15	27	11	3.1	5.4	5.3
7	19	-	4.6	>30	>30	3.2	13	13
8a	22	54	6.1	20	23	5.2	6.9	9.2
b	5.2	50	5.2	22	19	4.1	7.4	6.5
Normal values	11-36	5-45	UD-9.0	20-42	20-38	UD-7.0	4-18	4.5-21

Table 14



Correlation between arterial oxygen tension and serum testosterone in patients with restrictive lung disease ($r = 0{\cdot}682$, $p < 0{\cdot}05$).

FIGURE 18

Anterior pituitary function in man with hypoxic pulmonary fibrosis. Basal thyroid function: TSH and prolactin response to injected TRH

Patient	Basal serum T_3 (nmol/l)	Basal serum T_4 (nmol/l)	Serum TSH response (mU/l)			Serum Prolactin response (mU/l)		
			0'	30'	60'	0'	30'	60'
1	2.4	130	3.4	6.9	4.6	410	990	560
2a	1.8	110	1.9	9.9	5.3	110	220	110
b	1.7	55	5.9	31	20	590	820	690
3	2.1	90	2.1	11	9.4	78	350	230
4	1.4	75	1.2	5.8	4.3	250	530	450
5	2.3	72	2.1	14	8.9	250	840	520
6	2.1	108	1.6	6.1	4.4	110	260	150
7	1.7	82	2.3	16	17	98	440	2600
8a	1.6	70	3.7	12	11	200	760	630
b	1.6	123	2.6	12	8.9	300	580	380
Normal range	0.9-2.8	55-144	UO-8.0	Increment>3.6 30'>60'		60-360	Increment>65% of basal 30'>60'	

Table 15

Basal serum prolactin was moderately elevated in subjects 1 and 2b. There was a delayed prolactin response to injected TRH in subject 7.

DISCUSSION

We have demonstrated in hypoxic restrictive lung disease that hormone changes are essentially similar to those we have already reported in chronic obstructive airways disease (COAD)[139,148,149,156]. In each serum testosterone tends to be low in proportion to the level of hypoxia and not to that of SHBG which is normal or modestly elevated. These elevated levels may be secondary to low serum testosterone and would tend to reduce the free testosterone values even further. Suppression of the H-P-Testicular axis has again been demonstrated but in some RLD patients the disturbance appears to originate at pituitary rather than hypothalamic level, as evidenced by a diminished response of both LH and FSH to injected GnRH in patients 3 and 4. In COAD patients[149] LH responses were normal suggesting hypothalamic rather than pituitary suppression in that situation. Whether the hypothalamus or pituitary or both simultaneously are suppressed is difficult to determine. Conceivably following prolonged hypothalamic suppression producing chronic hyposecretion of GnRH the anterior pituitary might fail temporarily to respond to injected GnRH. A similar situation to this occurs in longstanding adrenocortical insufficiency secondary to pituitary ACTH deficiency where an ACTH stress test may produce a poor cortisol response misleadingly suggesting primary adrenal insufficiency. Thus poor LH and FSH responses to injected GnRH while suggesting pituitary suppression may still be compatible with a hypothalamic lesion. Accepting that the anterior pituitary itself may be suppressed it is of some interest that the organ lacks a direct blood supply being dependant on a portal blood supply. This seems to contribute to the

ischaemic pituitary damage caused by hypotension in obstetric bleeding (Sheehan's syndrome)[161] but whether this precarious blood supply predisposes the gland to hypoxic damage is speculative.

Subject 5, a comparatively young man, had high basal LH and FSH values (table 14) in the presence of normal serum testosterone, a picture seen in primary testicular failure as in Klinefelter's syndrome and sometimes in elderly men[143]. This man was taking cyclophosphamide as treatment for pulmonary fibrosis (table 21) and this drug damages testicular germinal (Sertoli) cells with subsequent oligospermia[162] though normal endocrine function is preserved at least in young men[163]. Therefore it seems possible though unlikely that this drug was responsible for the high gonadotrophin levels in this case. The presence of high gonadotrophin levels is not a feature we have noticed previously in hypoxic chest subjects though it is known that acute exposure to hypoxia at high altitude can induce changes in the testicular germinal epithelium of animals[118] and oligospermia in rams[164] and men[116] and that urinary output of testosterone after injection of human chorionic gonadotrophin is decreased in high altitude natives[112] suggesting the possibility of direct testicular suppression in that situation. However a fall in LH has also been noted in acute exposure to high altitude[114] and so it seems that we may have to recognise the possibility that either the hypothalamus, the pituitary or the testis alone may be on occasion the primary target organ for hypoxic injury.

In both of these chronic lung conditions, serum testosterone levels tend not to fall below normal until the PaO_2 drops below 7.3kPa (55mmHg)[139,148,149,156]. The four RLD patients with lowest testosterone and lowest PaO_2 values have each died by the time of writing so it appears that low serum testosterone gives an indication of prognosis in this condition and this also was the impression in

our COAD patients.

Unlike subject 2, subject 8 retained normal LH and FSH responses as his condition deteriorated with falling PaO_2 but by this time he was in hospital receiving intermittent oxygen therapy which may, if our postulate is correct, have improved H-P-T function.

In our studies to date we have found nothing to contradict the hypothesis that hypoxia is the offending agent accounting for the hormone changes. Certainly hypercapnia, present in many of our COAD patients with H-P-T suppression, cannot be incriminated as it was absent from all our RLD patients. There was no evident association between serum testosterone levels and bicarbonate or pH values (table 13). Corticosteroid suppression of the H-P-T axis has been described in Cushing's disease[165] but we have no reason to believe that steroid therapy is responsible in hypoxic chest disease. Our own (unpublished) observations suggest that even at a 50mg daily dose of prednisolone patients with non-endocrine disease retain normal testosterone values. Moreover subject 4 had low serum testosterone and was on no drugs (table 21) and amongst our hypoxic COAD subjects with low serum testosterone few were taking oral steroids. In addition we have noted a marked increase in serum testosterone in patients recovering from cor pulmonale[156] commensurate with a rise in PaO_2 despite the fact that such patients were often taking few if any drugs on admission in the acute phase but on recovery were on a number of drugs including spironolactone which has been alleged to reduce serum testosterone[166].

As in patients with COAD[139,149] it appears that the hypothalamo-pituitary-thyroid axis is comparatively well preserved in RLD although we did find in both syndromes the occasional instance of delayed TSH response to injected TRH (tables 12 and 15). Similarly

occasional instances of non drug induced modest prolactin elevation were found in both conditions (tables 10 and 15) but these are known to occur with any physical or emotional stress and drugs used were not ones usually associated with increased levels of prolactin[167].

Whether non-respiratory hypoxia also influences testosterone production will be explored in the next section.

CHAPTER X

ENDOCRINE FUNCTION IN CYANOTIC CONGENITAL HEART DISEASE[168]

Individuals with cyanotic congenital heart disease show normal testosterone and other hormone values perhaps because these subjects are acclimatised to hypoxia from birth unlike COAD and RLD patients but like high altitude natives. Alternatively endocrine differences may be related to differences in sleep stage patterns.

INTRODUCTION

After communicating our findings of depressed hypothalamo-pituitary-testicular axis in hypoxic chronic obstructive airways disease at the Thoracic Society[157] doubts were expressed as to whether hypoxia was indeed the adverse influence. It was held that some other aspect of blood gas status could be responsible though this now appears not to be the case according to more recent work (Chapter VIII). However the possibility remained that the endocrine abnormality was a function of lung disease rather than specifically of arterial oxygen status and so we decided to study hypoxic patients without lung disease choosing patients with cyanotic congenital heart disease (CCHD).

METHODS

Seven male outpatients with known CCHD were chosen from two cardiology clinics. Severity of breathlessness and arterial blood gas measurements were made as previously described. Pituitary function was assessed between 10.30am-12midday as detailed earlier. Correlation between serum testosterone and arterial oxygen tension was tested by a least sum of squares linear fit and statistical comparisons of hormone levels between patients and controls were made using Wilcoxon's rank test.

RESULTS

Clinical details of patients are presented in table 16. Four patients had grade 2 dyspnoea (breathlessness walking with person of own age on level ground) and three had grade 3 dyspnoea (stopping for breath when walking at own pace on level ground). All patients were hypoxic (PaO_2 range 5.7kPa;43mmHg - 7.1kPa;53mmHg) and normocapnic. Serum testosterone and other hormone values were in the normal range and in no case differed significantly from normal controls (table 17). Basal levels of LH, FSH, TSH and prolactin were normal in all patients though mean values of TSH were significantly higher ($p<0.05$) in patients than controls (table 18). Patient No 5 had an impaired FSH response to injected GnRH while patient No 7 had impaired LH and FSH responses (table 19). All patients had normal TSH and prolactin responses to TRH. Mean responses of LH, FSH TSH and prolactin were similar to those of controls (table 18).

DISCUSSION

This study demonstrates that endocrine status of cyanotic congenital heart disease subjects is not compromised to the same degree as it appears to be in hypoxic chronic obstructive airways disease and in restrictive lung disease. In figure 19 the lack of an association between arterial oxygen tension and serum testosterone in CCHD is clearly shown which is in marked contrast with the significant association in the case of both COAD and RLD where the slope of the regression lines are remarkably similar. If one considers the thirteen patients with respiratory disease whose PaO_2 values fell within the same range as that of the CCHD patients (5.7-7.1kPa), nine of the thirteen had subnormal values whereas all

Clinical details and arterial blood gas tensions in seven men with cyanotic congenital heart disease

Subject	Age (yr)	Heart disease	Grade of dyspnoea	PaO_2 (kPa)	$PaCO_2$ (kPa)	pH	Base excess (mmol/l)	Drugs prescribed
1	18	VSD-Eisenmenger's syndrome	2	5.7	4.4	7.48	+2	Verapamil
2	21	Tetralogy of Fallot	2	7.1	3.7	7.39	0	-
3	34	VSD-Eisenmenger's syndrome	3	6.4	3.9	7.49	0	-
4	27	ASD	2	6.3	4.0	7.39	-5	-
5	24	*Eisenmenger's syndrome	2	5.9	4.1	7.46	-1	Diazepam
6	29	*Eisenmenger's syndrome	3	6.1	4.1	7.39	-5	Allopurinol
7	44	VSD-Eisenmenger's syndrome	3	6.1	6.0	7.32	-1	Theophylline, dipyridamole
Normal values				10.7-13.3	4.7-6.0	7.36-7.44	±3	

VSD = Ventricular septal defect; ASD = Atrial septal defect; * = Site of shunt not known

Table 16

Various serum hormone levels of seven male patients with cyanotic congenital heart disease compared with those of age matched controls

	Serum					
	Testosterone (nmol/l)	SHBG (nmol/l)	Androstenedione (nmol/l)	DHAS (μmol/l)	T_4 (nmol/l)	T_3 (nmol/l)
Patients						
Mean	20.6	33.0	4.1	3.9	80.7	2.1
Standard deviation	5.2	21.0	1.2	3.2	9.4	0.5
Controls						
Mean	21.4	25.4	5.0	8.2	97.0	2.4
Standard deviation	3.3	8.9	1.3	4.8	19.1	0.3
Normal range	11-36	5-45	2-11	2-9	55-144	0.9-2.8
Significance of difference between the means*	NS	NS	NS	NS	NS	NS

* = Statistics using Wilcoxon's rank test

Table 17

Various pituitary hormone responses to injected gonadotrophin releasing hormone in seven male cyanotic congenital heart disease patients compared with those of age matched controls

	Serum											
	LH response (U/l)			FSH response (U/l)			TSH response (mU/l)			Prolactin response (mU/l)		
	0'	30'	60'	0'	30'	60'	0'	30'	60'	0'	30'	60'
Patients												
Mean	4.0	30.2	27.0	2.4	6.1	6.7	3.2	17.9	12.7	298	791	578
Standard deviation	0.8	13.0	9.2	0.6	3.3	4.1	0.5	5.8	6.1	98	308	265
Controls												
Mean	4.3	24.0	20.1	2.5	6.3	5.9	2.7	18.0	13.8	245	940	552
Standard deviation	2.1	4.3	2.4	0.7	2.6	2.3	0.9	4.1	5.5	83	590	339
Normal range	UD-9.0	20-42	20-38	UD-7.0	4-18	4.5-21	UD-8.0	Increment>3.6 30'>60'		60-360	Increment>65% of basal 30'>60'	
Significance of difference between the means*	NS	NS	NS	NS	NS	NS	p<0.05	NS	NS	NS	NS	NS

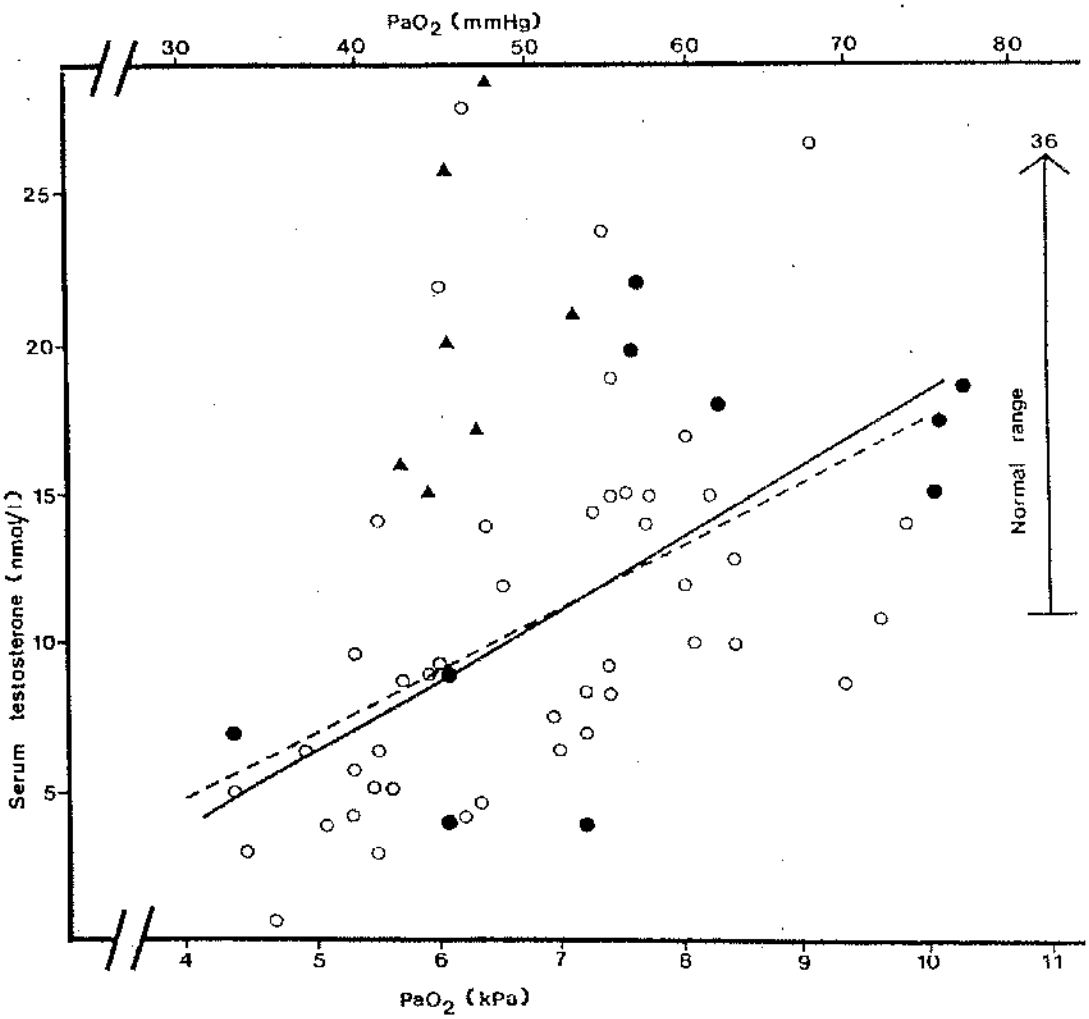
* = Statistics using Wilcoxon's rank test

Table 18

Responses of LH and FSH to injected GnRH and TSH and Prolactin to injected TRH in seven male cyanotic congenital heart disease patients

	Serum											
	LH response (U/l)			FSH response (U/l)			TSH response (mU/l)			Prolactin response (mU/l)		
	0'	30'	60'	0'	30'	60'	0'	30'	60'	0'	30'	60'
Patients												
1	3.8	34	26	3.1	10.0	9.7	2.8	18.0	8.6	288	691	399
2	5.7	41	35	2.7	4.8	5.0	2.7	20.0	15.0	362	942	788
3	3.4	20	23	3.1	6.5	7.5	2.8	8.7	6.8	406	813	812
4	3.5	35	29	2.7	11.0	14	3.8	25.0	25.0	418	1403	960
5	3.4	21	18	1.6	2.8	2.8	3.6	19.0	10.0	212	566	305
6	3.8	49	42	1.6	5.2	5.1	3.6	23.0	14.0	171	632	370
7	4.1	12	16	2.2	2.8	2.5	3.1	12.0	9.2	231	493	414
Normal range	UD-9.0	20-42	20-38	UD-7.0	4-18	4.5-21	UD-8.0	Increment>3.6 30'>60'		60-360	Increment>65% of basal 30'>60'	

Table 19



Correlation between arterial oxygen tension and serum testosterone in patients with COAD (○ - - - -, $r=0{\cdot}473$, $p<0{\cdot}01$), restrictive lung disease (● ——, $r=0{\cdot}682$, $p<0{\cdot}05$) and cyanotic congenital heart disease (▲, NS).

FIGURE 19

the CCHD patients had mid-normal values. The mean value of serum testosterone for the seven CCHD patients was double that of respiratory patients within the same PaO_2 range (CCHD 20.6±5.3; COAD 10.7±7.1; Significance of difference $p<0.05$).

CCHD patients tended to be younger than respiratory patients (CCHD mean = 28 years; COAD = 58 years; RLD = 51 years) which might explain the difference in H-P-T function if younger patients are better able to withstand the effects of hypoxia. However in normal men serum testosterone values do not substantially fall until after the age of 70[143]. Nevertheless it seemed appropriate to look retrospectively at our forty-five stable COAD patients (figure 8) to determine whether age contributed to testosterone depression. Twenty-two patients were aged less than 58 (age range 37-57 years) and twenty-three were aged more than 58 (age range 59-70 years). Arterial oxygen tensions were similar in each group (younger mean 6.91kPa±1.49;older mean 6.66kPa±1.26;NS) as were serum testosterone values (younger mean 9.68mmol/l±4.49;older mean 11.88mmol/l±7.51;NS). If ageing were an important factor we would have expected the older patients to have had lower testosterone values for a similar reduction in PaO_2.

At first glance this study suggests that hypoxia cannot be considered responsible for a suppressive influence on the H-P-T axis and that in respiratory disease another explanation should be sought. However as mentioned in Chapter III acute exposure to high altitude produces a reduction in urinary 17-ketosteroids suggesting low testosterone secretion[82,97,100,112] but high altitude natives retain comparatively normal values[94,113]. Conceivably as the CCHD patient is hypoxic from an early age he may resemble from the endocrine standpoint the high altitude native while the

respiratory patient who develops hypoxia usually in middle age may be more akin to the visitor to high altitude. The H-P-T axis may become "acclimatised" to hypoxia if exposed to it from an early age.

There may be yet another explanation for the difference between CCHD and respiratory patients. Recent studies of COAD patients have shown pronounced nocturnal dips of PaO_2 which are associated with the phases of rapid eye movement (REM) sleep[169,170] which seem to be an exaggeration of a normal response[171]. Douglas and colleagues in Edinburgh[170] consider that these hypoxic episodes, which may be profound with oxygen saturation dropping from 81 to 38%, may contribute to the development of pulmonary hypertension and secondary polycythaemia. There is a diurnal variation of plasma testosterone[172] with a maximal increase of about 30% at 5am, of prolactin[173,174] with a maximal nocturnal increase of about 50% and also of FSH though probably not of LH[175]. All these hormones demonstrate episodic release patterns with LH and prolactin peaks preceding testosterone peaks by about 60 minutes[176]. Recently testosterone cycles have been related to sleep stages with troughs in the middle of non-REM sleep and peaks near the non-REM REM junction[176]. As LH and testosterone cycles are related in time and as testosterone cycles are related to sleep cycles it would seem likely that sleep stage phases exert an influence on sex hormone production. It is not known whether LH cycles are related directly to sleep phases but if LH peaks occurred during REM sleep the severe hypoxia of REM sleep in COAD might have a major suppressive influence on gonadotrophin production and hence testosterone secretion. The Edinburgh group quote other authors who have shown that hypoxic dips during REM sleep occur in respiratory diseases other than COAD but recently they themselves have shown that these dips surprisingly do not occur in CCHD[177]. Interestingly profound hypoxic dips during

REM sleep also occur in men acutely exposed to high altitude[178]. Possibly then differences in sleep pattern behaviour between lung disease, altitude and CCHD might in due course prove to be an explanation for these apparent discrepant hormone findings.

Serum androstenedione values in CCHD patients did not differ from normal which was not surprising as in an earlier study in COAD normal values were noted with no change with recovery from cor pulmonale[156]. On the other hand mean serum DHAS in CCHD patients was less than half that of normal controls though this difference just failed to reach significance. Interestingly this adrenal androgen was earlier shown to be significantly lower in blue bloaters than in pink puffers[139] and the fact that it rose with recovery from cor pulmonale[156] suggests that it may indeed be suppressed by hypoxia.

Clearly there is scope for further research in this area. The next four chapters deal with adverse effects of hypoxia which have been studied.

CHAPTER XI

SEXUAL IMPOTENCE IN HYPOXIC CONDITIONS[159,160,168,179,180]

Hypoxic patients with chronic obstructive airways disease and restrictive lung disease were found to have diminished libido and evidence of organic sexual impotence which contrasted with normal sexual function in men with cyanotic congenital heart disease and comparable hypoxia. Evidence is offered that sexual activity varies with changes in severity of disease, arterial oxygenation and testosterone values. The contrast in sexual activity between these clinical groups can be explained largely by differences in testosterone status.

INTRODUCTION

We have shown that serum testosterone levels are depressed in hypoxic lung disease[139,148,156,159,160] and have furnished evidence that this is probably due to depression of the H-P-Testicular axis by hypoxia. Part of the evidence is the finding that this hormone level varies with the disease severity and with the consequent PaO_2 level. It seemed possible that such patients might have altered sexual function though remarkably little work had been undertaken in this field and we therefore set out to find how this variable hormone abnormality affects sexual function in patients with hypoxic COAD, RLD and CCHD.

As part of the projects studying endocrine aspects of these conditions[159,160,168,179] we also made enquiries about sexual function. For reasons of clarity results of sexual studies in the various conditions have been brought together in this chapter.

METHODS

PATIENTS - Ten patients with COAD were studied. Four of these were inpatients with exacerbations of cor pulmonale (table 20: patients No 1-4) and six consecutive stable bronchitic outpatients (table 20: Nos 5-10). All were married and ages ranged from 36-60 years. Criteria of COAD were as previously described (Chapter I). Eight patients with RLD with an age range of 35-72 years (table 21) are those detailed in Chapter IX. Seven patients with CCHD with an age range of 18-44 years (table 22) have been described in Chapter X.

ASSESSING SEXUAL FUNCTION - Nocturnal erections during rapid eye movement (REM) sleep occur even in neonates[181] and early morning erections (EME's) are related to the last REM sleep of the night. Their absence is taken as a reliable guide in distinguishing organic from psychological impotence[181,182]. In fact Karacan and colleagues[182] in a study of more than 2,000 men found none who had normal sexual function without such erections. According to Kinsey and colleagues[183] EME's usually persist for some years after loss of sexual activity and their absence suggests long standing organic impotence. We made our assessments of sexual function from answers to questions related to sex drive (libido) and to coital frequency and performance as well as the frequency of EME's. In unmarried men we enquired about masturbatory habits and the occurrence of nocturnal emissions.

RESULTS

COAD patients No 1-4 (table 20) were studied in hospital while in respiratory failure when mean PaO_2 was 5.5kPa and again when stable four months later when mean PaO_2 had risen to 7.6kPa. The other six COAD patients had a mean PaO_2 of 6.0kPa. Of the ten

Sexual function in hypoxic men with chronic obstructive airways disease

Patient	Age (years)	Dyspnoea grade	PaC_2 (kPa)	Serum testosterone (nmol/l)	Diminished libido?	Time since last sexual intercourse	Erectile difficulty?	Early morning erection?
1	50	4	4.8 (when well 5.6)	6 (when well 9)	Yes - 18 months	2 months	Yes	No - 18 months
2	36	4	5.2 (when well 7.3)	6 (when well 19)	Yes - when chest bad	3 months	When chest bad	Not when chest bad
3	53	4	5.2 (when well 9.2)	4 (when well 9)	Yes - 10 years	4 months	No	No - years
4	52	4	6.9 (when well 8.3)	7 (when well 13)	Yes - 3 months	3 months	No	No - years
5	57	4	5.2	10	Yes - 10 years	3 months	Yes	No - many years
6	60	3	6.4	12	Yes - 3 years	3 years	Yes	No - 2 years
7	43	3	5.6	22	No	Recent	No	Yes - frequent
8	54	3	7.6	18	Yes - 10 years	6 weeks	Yes	Yes - occasional
9	53	4	4.9	15	Yes - 3 years	3 years	Yes	No - 2 years
10	50	3	6.3	9	Yes - when chest bad	4 months	When chest bad	No - 4 months

Table 20

Sexual function in hypoxic men with restrictive lung disease

Patient	Age (years)	Dyspnoea grade	PaO_2 (kPa)	Serum testosterone (nmol/l)	Diminished libido?	Time since last sexual intercourse	Early Morning erection?	Drug history
1	35	4	6.1	9	NA	-	-	Prednisolone 40mg
2a	45	3	8.3	18	Yes 3years	1month	No 2years	Nil
b	"	4	6.1	4	"	6months	"	Prednisolone 10mg, digoxin 0.25mg, frusemide 40mg, spironolactone 200mg
3	59	3	9.9	15	No	1month	No ?years	Nil
4	72	4	7.2	4	NA	-	-	Nil
5	50	4	7.6	20	Yes 7months	7months	No 6months	Prednisolone 10mg, cyclophosphamide 60mg
6	41	4	10.1	18	Yes >1year	1month	No >1year	Nil
7	53	1	10.3	19	No	Recent	Yes	Nil
8a	56	4	7.7	22	Yes 6months	2weeks	Less regular	Nil
b	"	4	4.4	5	"	>3months	No	Prednisolone 40mg, azathioprine 200mg, bendrofluazide 10mg

NA = Not asked

2a, 2b and 8a, 8b = Patients studied on two separate occasions

Table 21

Sexual function in men with cyanotic congenital heart disease

Patient	Age (years)	Dyspnoea grade	PaO_2 (kPa)	Serum testosterone (nmol/l)	Marital status	Diminisned libido?	Early morning erection?	Sexual activity
1	18	2	5.7	16	Unmarried	No	Yes	No SI; no masturbation; has nocturnal emissions
2	21	2	7.1	21	"	No	Yes	No SI; masturbation normal
3	34	3	6.4	29	"	No	Yes	No SI; no masturbation; has nocturnal emissions
4	27	2	6.3	17	Married	No	Yes	SI daily; fertile
5	24	2	5.9	15	"	Yes	No - recently	SI daily, fertile; dyspnoea at SI
6	29	3	6.1	26	"	No	No - never	SI x 2 per week; fertile; temporary impotence 1978
7	44	3	6.1	20	Divorced	No	Yes	No SI since divorced; SI was normal; infertile marriage

SI = Sexual intercourse

Table 22

COAD patients serum testosterone levels were low in six, towards the lower end of the normal range in two while two others (Nos 7 and 8) had mid-normal values. Patients No 1-4 showed a doubling of mean serum testosterone values four months after discharge from hospital. All, apart from No 7, admitted to reduced sexual activity varying in duration from three months to ten years. Some were relieved by this questioning as lack of sex drive had been a source of anxiety even although none had sought advice about it. All suffered from severe dyspnoea on occasions but they were convinced that decreased sexual activity was mainly due to lack of libido rather than to the prospect of effort dyspnoea at intercourse. Two had not had sexual intercourse for three years or more: six did have intercourse at intervals of approximately 3-4 months and two more frequently than this. Difficulty in obtaining an erection was variable, being a permanent problem in five while in two patients the problem was only encountered when their "chests were bad". Early morning erections were absent in seven patients and only occasionally happened in one while in another man they occurred only when his "chest was good". Interestingly libido levels and EME activity were sometimes noted to vary with alterations in severity of the chest condition. Patients 1-4 (table 20) who were asked while in hospital with respiratory failure about sexual activity prior to admission were reviewed four months later. They were asked what changes in sexual activity had occurred and three of them had noted progressive improvement. Patient No 2 was now having almost daily coitus and EME's had returned: No 3 was having coitus almost fortnightly with occasional EME's while in the case of No 4 it was occurring almost monthly but without EME's.

Of the eight pulmonary fibrosis (RLD) patients four had frankly

low serum testosterone values (table 21). Of the six married men under the age of 70 four admitted to diminished libido for periods of six months to three years accompanied by infrequent or absent EME's while subject No 3 had normal libido despite absent EME's for years. In those with suppressed libido coitus was infrequent and when achieved tended to be unsatisfactory with unsatisfactory or absent orgasm. Diminished libido did occur in individuals with normal serum testosterone values and the prospect of dyspnoea induced by coitus often played some part in suppressing libido.

Of the seven patients with cyanotic congenital heart disease all had normal serum testosterone levels (table 22) and only one (No 5) had noticed slight recent decrease in libido with absent EME's though he still performed almost daily coitus. The other six had healthy libido but subject No 6 had never known EME's though he had normal coitus twice weekly. It is unfortunate for the purposes of this study that four of the seven were unmarried and thus unsuited to provide a relevant coital history. However their experiencing EME's and nocturnal emissions is good evidence that organic impotence was not present.

DISCUSSION

AGE - A number of factors have to be considered as possible contributors to the sexual impairment now shown to occur in hypoxic lung disease. Our subjects questioned regarding sexual function were all aged 60 years or less and so the great majority would have been expected to be sexually active. Indeed it has been shown that 90% of men aged 50-60 years do practice regular coitus or can provide other evidence of sexual activity[183-5]. Clearly there must be a gradual decline of such activity over the years but we have been

interested rather in the possibility of more dramatic changes than this and our finding of reversible impotence in COAD patients recovering from cor pulmonale shows that such changes can occur.

DYSPNOEA - Anticipation of dyspnoea during intercourse was thought by a few but not all impotent COAD and RLD patients to be a factor in reducing libido. However seven of the ten former patients and five of the six in the later group who were questioned had absent EME's as good evidence of organic impotence.

DRUGS - Medicines commonly taken for the management of COAD including corticosteroids, theophyllines and sympathomimetics do not affect sex function[186]. Others in general use such as sedatives, tranquilisers, antihypertensives, antidepressants[186], bendrofluazide[187] and occasionally cimetidine[188] may cause impotence. Phenothiazines are capable of lowering serum testosterone levels[189]. However our patients with low serum testosterone levels or impotence were seldom if ever taking such drugs (tables 10,21) and so it seems unlikely that drugs are important here. Moreover patients recovering from cor pulmonale showed increases in serum testosterone levels and improvement in sexual function despite being on more drugs than when admitted to hospital in the acute stage[156,179].

HYPERPROLACTINAEMIA - This is associated with low serum testosterone[190], low LH and impotence and though our pilot study did indicate occasional high prolactin levels in COAD (table 10) this appears not to be common and certainly not a causal factor in the organic impotence of pulmonary disease (tables 12,15).

PSYCHOLOGICAL EFFECTS - Frustration, anxiety and depression are common features in chronic respiratory insufficiency. Agle and Baum[191] studying psychological aspects of COAD noted seventeen out of twenty-three patients to have significantly depressed mood and to have reduced

libido and diminished erectile ability. Six had been totally impotent for longer than one year. Dyspnoea of intercourse and easy fatiguability were usually blamed for these symptoms. Psychiatric rehabilitation produced improvement in sexual function in only one patient and the authors concluded that either the impotence had a physical basis or psychological methods of treatment were inadequate. No endocrine or other physical basis for impotence was postulated. Whereas traditionally impotence has been labelled organic or psychological, recently it has been suggested that it is wrong to categorise patients strictly as many patients show both traits and there may be complex interactions between physical and psychological influences[192,193]. To date we have not studied psychological aspects of these diseases though readily accepting that psychological factors could well be relevant here.

DEBILITY AND FATIGUE - As with depression it is difficult to imagine that such general effects of the illness when severe will not have some adverse effect on libido and sexual performance.

TESTOSTERONE DEFICIENCY - That low testosterone levels may cause male impotence is generally accepted[194,195] and the view that low serum testosterone levels rather than debility of illness itself is the major factor affecting sexual behaviour in patients with respiratory hypoxia is supported by the fact that three patients with the highest serum testosterone values in the COAD study (table 20: No 2 when well, Nos 7 and 8) were ones who experienced regular EME's.

While many factors such as ageing, depression, fatigue, debility, dyspnoea and drugs can affect libido and sexual activity,

we have now obtained evidence from these chronic bronchitic as well as the pulmonary fibrosis patients that they are indeed affected by impotence which is at least partly organic in nature. Thus nine of the ten COAD patients had impaired sexual function with absent EME's in seven while in the eight RLD subjects they were absent in five. Especially in the former group, some were well aware of sexual activity and performance increasing as they improved clinically and of course it was at these times that we were able to demonstrate rising serum testosterone levels along with increasing arterial blood oxygenation.

To understand why similarly hypoxic congenital heart disease subjects have normal sexual function and serum testosterone levels we have to remember the extraordinary physiological differences between dwellers in the high Andes and immigrant visitors from the plains. Like these high altitude natives, CCHD subjects may be 'acclimatised' to hypoxia. Acquired tolerance to hypoxia at birth may explain their normal gonadal endocrine and sexual function.

Despite our publication in 1980[179] a recent American paper[196] with associated editorial[197] claimed to be the first to describe organic sexual impotence in COAD sufferers. Impotent patients were more hypoxic than the non-impotent and as in our study there was evidence of improved sexual function with improved respiratory status. Not surprisingly we were quick to point out that our earlier studies had already highlighted the problem[198].

CHAPTER XII

METABOLIC CHANGES IN CHRONIC OBSTRUCTIVE AIRWAYS DISEASE[156]

Low TBK in cor pulmonale fell further with recovery reflecting in part a continuing fall in lean body mass. Intracellular water appeared to increase despite each of the other lean body mass indices falling with recovery, a result thought to be spurious and due to isotope equilibration problems perhaps caused by hypoxia. Fluctuations in anabolic steroid production seem not to influence changes in lean body mass in this situation.

INTRODUCTION

Campbell and associates[75] suggested that body tissue is lost rapidly by patients during exacerbations of cor pulmonale. This tissue, sometimes called lean body mass (LBM) or fat-free mass (FFM) was claimed to increase with recovery. Accumulation of oedema in cor pulmonale and dispersal of it during recovery were not accompanied by the expected changes in total body weight and might have been due to redistribution of fluid between intracellular and extracellular compartments. We performed similar metabolic studies during acute stage cor pulmonale and again after recovery to discover whether loss of LBM is related to the anabolic steroid suppression previously demonstrated (Chapter VIII)[156].

PATIENTS

The seven male patients were those studied in Chapter VIII, the endocrine and metabolic studies being performed concurrently. Investigations were commenced three or four days after they were admitted to hospital in cor pulmonale failure and were repeated some months after recovery. Measurements made were total body potassium (TBK),

serum potassium, serum sodium, total body water (TBW), extracellular water (ECW), intracellular water (ICW), total body weight, dry body weight and fat-free mass (Chapter I).

RESULTS

Improvement in arterial blood gas and in sex hormone status with recovery from acute stage cor pulmonale has been detailed previously (figures 14,15 and 16). Though mean values for body weight did not change significantly with recovery (table 23) five of the seven patients continued to lose weight, especially two who were on reduction diets. Group mean TBW and dry body weight did not change significantly, though the latter fell in six men. A similar pattern was observed for ECW, while ICW increased with recovery ($p<0.05$). The group's mean TBK remained unaltered, though when expressed as a percentage of predicted normal the values were low ($p<0.005$), with a further fall on recovery ($p = 0.05$). Intracellular potassium values, which were normal in the acute phase, fell significantly ($p<0.02$) to subnormal with recovery. Serum potassium and sodium remained normal throughout (table 24).

Table 24 lists values for FFM obtained by the four different methods — skinfold thickness, TBK, TBW and "predicted". The TBK method gave the lowest value but none of the group mean FFM values obtained by the four techniques differed significantly from each other. When the changes in FFM between the acute phase of the illness and recovery determined by each of the four methods were compared, the skinfold thickness method agreed closely with the TBK and "predicted" methods but the TBW method correlated poorly with each of the others. Comparison of predicted FFM values with those obtained by the skinfold method never showed more than an 8%

Changes in body weight and body compartments between acute cor pulmonale and recovery

Subjects	Weight (kg)	TBW (l)	TBW measured / TBW predicted (%)	Dry body weight (kg)	ECW (l)	ECW measured / ECW predicted (%)	ICW (l)	ICW measured / ICW predicted (%)	TBK (mmol)	TBK measured / TBK predicted (%)	ICK (mmol)
Acute cor pulmonale											
1	78.9	36.5	88	42.4	16.8	91	19.7	85	2848	79	145
2	49.5	28.8	96	20.7	14.8	133	14.0	74	2094	91	150
3	103.8	46.5	94	57.3	22.1	108	24.4	85	3773	93	155
4	63.4	39.7	114	23.7	20.5	134	19.2	99	2726	94	142
5	63.8	36.1	105	27.7	17.2	110	18.9	102	2358	81	125
6	59.6	34.1	107	25.5	14.6	107	19.5	107	2550	100	131
7	74.5	37.0	93	37.5	16.8	86	20.2	100	2956	82	146
Mean	70.5	36.9	100	33.5	17.5	100	19.4	93	2757	89*	142
Recovery											
1	69.8	37.1	96	32.7	14.0	81	22.8	109	2415	71	106
2	47.2	28.1	96	19.1	13.0	113	15.5	85	1945	85	125
3	96.7	51.6	100	45.1	21.1	107	30.5	113	3378	86	111
4	61.8	32.4	96	29.4	13.0	90	19.2	102	2276	82	119
5	60.8	37.2	111	23.6	16.3	106	20.9	116	2287	80	109
6	62.5	37.4	113	25.1	14.4	103	23.0	122	2538	95	110
7	78.9	42.4	103	36.1	18.1	91	24.3	115	3148	85	130
Mean	68.2	38.0	104	30.2	15.7	99	22.3	109	2569	83†	116
Significance of difference‡	NS	NS	NS	NS	NS	NS	p<0.05	p<0.02	NS	p=0.05	p<0.02

* = Significantly low (p<0.005)

† = Significantly low (p<0.001)

‡ = Statistics using Wilcoxon's test for paired differences

Table 23

Serum electrolyte values: comparison of fat-free mass measurements assessed by various techniques and indirect measurement of potassium concentration in fat-free mass altered between acute cor pulmonale and recovery

Subjects	Serum potassium (mmol/l)	Serum sodium (mmol/l)	FFM(SFT) (kg)	FFM(TBW) (kg)	FFM(TBK) (kg)	FFM(predicted) (kg)	ΔTBK/ ΔFFM(SFT) (mmol/kg)
Acute cor pulmonale							
1	4.5	137	54.8	50.0	49.4	59.0	106
2	3.3	141	39.2	39.4	43.8	41.2	71
3	3.8	140	65.3	63.6	56.5	68.6	208
4	4.9	143	53.1	54.4	48.6	50.6	59
5	3.6	137	48.5	49.5	45.8	51.1	-
6	4.4	138	46.1	46.7	47.3	47.4	-
7	3.6	135	54.9	50.7	50.3	59.3	64
Mean	4.0	139	51.7	50.6	48.8	53.9	
Recovery							
1	4.2	139	50.7	50.8	46.2	55.3	
2	3.4	131	37.1	38.5	42.7	40.2	
3	4.0	136	63.4	70.7	53.5	65.7	
4	4.9	135	45.5	44.4	45.2	49.4	
5	3.8	138	48.2	51.0	45.2	50.0	
6	4.1	139	47.8	51.2	47.1	48.6	
7	4.3	140	57.9	58.1	51.7	61.0	
Mean	4.1	137	50.1	52.1	47.4	52.9	
Significance of difference *	NS	NS	NS	NS	NS	NS	

FFM(SFT), FFM(TBW), FFM(TBK) and FFM(predicted) = Fat-free mass assessed from skinfold thickness, total body water and total body potassium and that predicted from height and weight; ΔTBK/ ΔFFM(SFT) = Change in total body potassium between cor pulmonale and recovery divided by change in fat-free mass.
* = Statistics using Wilcoxon's test for paired differences.

Table 24

discrepancy, whereas there were differences of up to 15% between predicted values and those obtained by the TBW and TBK methods.

For the five subjects (Nos 1,2,3,4 and 7) who showed a significant change (>±7%) in TBK the ratio $\Delta TBK/\Delta FFM$ (SFT) (change in total body potassium between cor pulmonale and recovery divided by change in fat-free mass) derived from the skinfold thickness method is included in table 24. The accepted value for potassium concentration in fat-free tissue is 69mmol/kg. For subjects 2,4 and 7 good agreement with this value was recorded, while subjects 1 and 3 showed potassium loss exceeding that which could be accounted for by loss of fat-free tissue.

DISCUSSION

From this study we can conclude that FFM continues to fall despite recovery from acute stage cor pulmonale and a rise in anabolic steroid production. Though TBW showed no consistent changes, dry body weight decreased in six men on recovery, but the group mean did not change significantly. The lack of reduction in TBW might seem surprising but this was not measured until about the fourth day of the acute illness, when oedema had largely dispersed. A rise of ICW and fall of ECW during recovery is consistent with the finding by Campbell and colleagues[75] of a fall in ICW with the onset of cor pulmonale oedema. They found no appreciable gain in weight at its onset and postulated that the fluid accumulation is due not to overall fluid retention but to a shift from the intracellular compartment. This conflicts with the recent finding by other workers[199] of decreased glomerular filtration rate and hypertrophied renal glomeruli in cor pulmonale. They on the other hand have suggested that renal handling of sodium and water in response to changes in PaO_2

is the principal abnormality leading to oedema in COAD.

Campbell and colleagues[75] suggested that the fall in ICW, which is usually accepted as an index of FFM[200] might be related to loss of lean tissue. If this were the case, our finding of a 10% rise in ICW with recovery might reflect a gain in FFM, perhaps caused by increased anabolic steroid production. We have reservations however about such a tidy explanation. The close relationship of ICW measured by isotope dilution to FFM is accepted in healthy individuals[201] but we doubt whether it is applicable in the present context. In addition the anomalous recovery increase in FFM assessed by body water isotope dilution is perhaps not surprising when it is appreciated that FFM cannot be calculated from TBW in patients with abnormal hydration[202]. The apparent increase in FFM might be explained by a waterlogging of cells so that the increase in ICW on recovery may not reflect a true increase in fat-free mass. Alternatively, the inconsistent rise in intracellular water on recovery may be due to an altered cell permeability to isotopes in the acutely hypoxic phase that gives false values for water compartments[203,204]. Clearly isotope dilution studies should be interpreted with caution in abnormal metabolic states.

The total body potassium method of assessing FFM, also well tried in normal individuals[205,206], requires normal intracellular potassium values and as we have shown in this study that these may be low this method of measuring fat-free mass may well be unreliable in our type of study. The other indices — FFM as assessed by the skinfold thickness and by the "predicted" methods (table 24) and dry body weight (table 23) — all suggest that lean tissue is lost gradually despite clinical stabilisation, which is consistent with slowly progressive clinical deterioration — 67% of these patients

dying within five years of their first episode of oedema[41]. The development of oedema in high altitude natives (Monge's disease) similarly carries a poor prognosis[207].

Using an isotope dilution method considered by others to be unreliable[125], Campbell et al[75] found inconsistent changes in TBK with recovery. Using the more reliable whole-body monitor method we found low TBK values during the acute illness with a further fall on recovery. Intracellular potassium concentrations assessed by dividing TBK by ICW fell to subnormal values but of course this is a genuine fall only if the increase in ICW accompanying recovery is a true one. If potassium, the main intracellular cation, were low, it would be replaced by sodium to a similar osmotic equilibrium. However the expected fall in serum sodium[208] did not occur (table 24) so these low intracellular potassium values may well result from spuriously high intracellular water measurements. Low total body potassium on the other hand could in part be due to reduction of fat-free mass and this may apply to patients 2,4 and 7 (table 24), in whom the loss of total body potassium was that expected from the degree of fat-free mass loss recorded. For the patients 1 and 3, other, as yet unidentified factors must contribute to the explanation of the excess potassium loss. It seems not due to diet[139] nor solely to diuretic treatment[131,209] and the role of hyperaldosteronism here is unknown.

This study demonstrates a fall in most of the indices of FFM with clinical recovery from severe cor pulmonale despite an increase in anabolic steroid production. The apparent rise in intracellular water with recovery is probably due to poor isotope equilibration in this hypoxic situation where there may have been falsely high extracellular water values and thereby spuriously low initial

intracellular water values. Even if the rise in intracellular water with recovery were genuine it apparently does not equate with increase in fat-free mass and may merely indicate cellular waterlogging. Our earlier finding of low total body potassium was confirmed and we believe this is only in part due to loss of fat-free mass. Clearly there is still much to be learned about this complex subject.

CHAPTER XIII

PITUITARY FOSSA ABNORMALITIES IN CHRONIC OBSTRUCTIVE AIRWAYS DISEASE[210]

Nine out of fourteen hypoxic men with chronic bronchitis were found to have erosive or porotic pituitary fossa changes on x-ray. Hypoxia but not hypercapnia was universally present. It is postulated that the mechanisms for these changes may involve low anabolic steroid production, raised intracerebral pressure and engorged intracranial blood vessels, each related to the hypoxia.

INTRODUCTION

Newton and colleagues[211] described seven patients with chronic bronchitis and associated chronic hypercapnia and one with intermittent hypercapnia, all of whom had radiological pituitary fossa abnormalities. Such an association had not previously been reported and they ascribed them to raised intracranial pressure caused by hypercapnia finding no such radiological changes among chronic bronchitic patients with normal arterial carbon dioxide tensions. They made no mention of arterial oxygen levels in patients or controls.

In view of our demonstration of previously unrecognised and potentially far-reaching hormonal effects of hypoxia in such patients[139,149,156,179] and in the knowledge that low androgen levels may cause osteoporosis[212] we set out to repeat the above study using demonstrably hypoxic chronic bronchitic patients, some with and some without hypercapnia, to determine whether or not such radiological changes are indeed related exclusively to the raised intracranial pressure of hypercapnia.

PATIENTS

Fourteen stable male out-patient chronic bronchitic patients

were chosen to represent a wide range of arterial blood gas tensions. Criteria for chronic bronchitis and airways obstruction were as previously described (Chapter I) and all had grade 3 or 4 dyspnoea[133]. No patient was having steroid treatment. Arterial blood gases were measured on two occasions at least two months apart by methods previously described. The severity of dyspnoea, pulmonary function results and arterial blood gas tensions are illustrated in table 25.

Each patient had a coned lateral radiograph of the pituitary fossa. Fourteen age-matched men who attended with head injuries had a similar coned radiograph taken in addition to the routine skull radiograph and acted as a control group. The films were read by a neuroradiologist who was not aware of the individual clinical state or blood gas measurements. The abnormalities were categorised as follows: A = thinning of the lamina dura; B = erosion of the lamina dura of the dorsum sellae; C = erosion of the floor of the pituitary fossa; D = general reduced density of the dorsum sellae. This method is identical to that used by Newton and colleagues[211] except for the addition of category D. The films were jumbled and reassessed at a second sitting and scores compared with those assigned at the first sitting. Films scored as normal or abnormal on both occasions were so classified. Where the two scores conflicted these doubtful films were again jumbled and rescored on two separate occasions. Where they had become 3:1 normal:doubtful they were called "probably normal" and where they were 2:2 or 1:3 normal:abnormal/doubtful they were called "probably abnormal". Statistical comparisons were made with the chi square test.

Summary of results of pulmonary function tests, arterial blood gas tensions, pituitary fossa x-ray appearances and smoking habit in male patients with chronic bronchitis

Case No	Age	FEV_1 (l)	FEV_1/FVC (%)	Grade of dyspnoea	Mean PaO_2 (kPa)	Mean $PaCO_2$ (kPa)	Pituitary fossa x-ray appearance	Smoking (cigarettes/day)
1	43	0.75	27	4	5.6	8.1	Normal	20
2	53	0.85	34	4	4.4	7.3	*B, C	15
3	51	0.5	50	4	5.5	8.9	Normal	Ex-smoker
4	50	0.9	60	4	5.3	7.3	*B	20
5	36	0.8	57	4	6.3	7.7	†A	60
6	57	0.8	66	4	5.6	7.6	‡Normal	Non-smoker
7	53	0.75	37	4	7.2	7.7	Normal	40
8	52	1.7	59	3	7.9	6.6	Normal	30
9	60	0.9	47	4	7.1	5.2	†A, C	40
10	62	2.25	64	4	9.3	4.7	*B	50
11	49	2.0	57	4	9.9	4.7	*B, D	40
12	54	1.8	58	4	7.5	5.7	†A	30
13	49	2.0	52	3	9.6	5.3	*B	20
14	57	0.65	65	4	9.2	4.5	*B	40

A = Thinning of the lamina dura; B = Erosion of the lamina dura of the dorsum sellae; C = Erosion of the floor of the pituitary fossa;

D = General reduced density of the dorsum sellae.

* = Definitely abnormal

† = Probably abnormal

‡ = Probably normal

Table 25

RESULTS

Of the 14 patients, six had abnormal and three had probably abnormal pituitary fossa films, whereas in the control group one patient had an abnormal and one a probably abnormal film. This is a significant difference ($p<0.01$). When this group was divided into those with normocapnia ($PaCO_2<5.9kPa;44mmHg$) and those with hypercapnia ($PaCO_2>5.9kPa$) all six of the normocapnic patients (Nos 9-14 in table 25) and three of the eight hypercapnia patients (Nos 2,4 and 5) had definite or probable abnormalities of the pituitary fossa on the x-ray film. (Examples of abnormal x-ray films are shown in the reprint).

The radiological features of sellar osteoporosis are lack of bone density (D) with thinning of the lamina dura (A), while erosion (interruption or disappearance) of the lamina dura (B and C) is the characteristic change resulting from raised intracranial pressure[213-215]. Abnormalities consistent with raised pressure were seen in seven of our nine patients in whom changes were noted. In two of these (Nos 9 and 11) abnormalities consistent with osteoporosis were also present, while the remaining two showed osteoporotic changes only.

DISCUSSION

Our finding of an increased prevalence of sellar lamina dura changes on skull radiographs of patients with chronic bronchitis confirms the original observation of Newton and colleagues[211]. While we agree that most of these radiological changes are in keeping with increased intracranial pressure, we have shown they are not an invariable accompaniment of chronic hypercapnia as was assumed in the original paper. Five of our eight hypercapnic subjects had

normal pituitary fossa appearances. In particular patients 1,3 and 6 had had arterial blood gases monitored for four years, confirming the chronicity of hypercapnia and the last of these, still without abnormalities of the pituitary fossa, had been admitted with headache and papilloedema caused by raised intracranial pressure on two occasions. All six of the normocapnic patients had definite changes or probable abnormalities. Interestingly, one control subject had definite and another probable pituitary fossa changes. These controls, however, were a random selection of men from an urban population attending for urgent skull x-ray examination and chronic bronchitis was not excluded.

Four of our patients showed distinctive radiological features of osteoporosis with lack of bone density or thinning of the lamina dura either accompanying erosive changes or on their own. It will be remarked that no patient had had steroid treatment. The table in the paper of Newton and colleagues shows that four of their 10 subjects also had thinning of the lamina dura, three with and one without additional erosive changes. No mention was made of osteoporosis and indeed no special reference was made to this finding it being accepted as one of the changes to be expected in patients with raised intracranial pressure.

As chronic hypercapnia apparently can no longer be accepted as the only or main cause of these pituitary fossa changes, we believe that chronic hypoxia merits consideration as the aetiological factor. All fourteen of these patients were hypoxic though there was no evident association between their present degree of hypoxia and prevalence of pituitary fossa changes. Nevertheless we consider that the osteoporotic changes might be related to chronic hypoxia itself or indirectly to the anabolic steroid suppression associated with it.

Another factor to be considered is cigarette smoking which was a feature of all the patients with abnormal pituitary fossa x-rays in this study. It has been shown that in men heavy cigarette smoking causes a modest fall in serum testosterone[158] and in women is associated with premature deficiency of sex hormones[216], premature menopause[217] and a high prevalence of osteoporosis after the menopause[218,219]. Whether smoking predisposes men to osteoporosis is not known.

Chronic hypercapnia is a potent cause of raised intracranial pressure and if we are correct in assuming that it is not responsible for the erosive changes in the sella turcica, we might reasonably question whether such radiographic appearances in this condition are indeed due to a general increase in intracranial pressure. Fry and du Boulay[214] found pituitary fossa changes identical to those of raised intracranial pressure in 7% of hypertensive patients and suggested two possible mechanisms: either raised intracranial pressure itself or local pressure from excessive vascular pulsation. Since hypoxia is known to raise intracranial pressure by enhancing cerebral blood flow[220] and to engorge intracranial blood vessels[221], perhaps these erosive changes of the sella turcica can be produced over years by local pressure from engorged pulsatile internal carotid arteries or engorged venous channels.

In conclusion, we believe that hypercapnia is not a prerequisite for the development of pituitary fossa changes in chronic bronchitis and suspect that hypoxia may be more important. Our findings suggest that osteoporosis may indeed on occasions be responsible for or contribute to the radiological abnormalities. Erosive changes, however, probably occur more frequently than porotic ones and may be caused by chronic excessive local vascular pulsatile pressure or by

general raised intracranial pressure. The mechanisms for the development of these pituitary fossa changes are complex and a search for further skeletal osteoporosis in hypoxic COAD might well be rewarding.

CHAPTER XIV

ABNORMALITIES OF CEREBRAL BLOOD FLOW IN SECONDARY POLYCYTHAEMIA[222]

Low cerebral blood flow (CBF) values in polycythaemic COAD subjects and in primary polycythaemics increased to a similar degree after venesection. In COAD symptomatic benefit was infrequent, cerebral oxygen delivery fell and H-P-Testicular function did not improve with increase in CBF.

INTRODUCTION

Our confirmation of a correlation between PaO_2 and red cell volume in randomly selected COAD patients (Chapter IV, figure 6)[131] combined with the knowledge that COAD is a common disease[223] suggests that secondary polycythaemia likewise is prevalent. Haematocrit and CBF are correlated even in normal people[224] and though little work has been carried out in the secondary polycythaemia of COAD it seems probable that reduction in CBF is common. It is well recognised that polycythaemic patients are prone to strokes and transient cerebral or other ischaemic episodes[225-227] and lowered CBF has been suggested as the cause. It is considered that reduced CBF is caused by increase in viscosity as a result of high haematocrit[228]. Lowering of haematocrit by venesection increases CBF in various types of polycythaemia[224,227,229,230] with apparent reduction in cerebral ischaemic effects[224,227]. In the secondary polycythaemia of COAD venesection may produce apparent subjective benefit[231] but little objective improvement[231-233] although here also CBF values have been shown to increase[230]. However as reduction of haematocrit also reduces oxygen carriage per unit volume of blood, cerebral oxygen delivery may not increase with rise in CBF and any benefit seems unlikely to be related to better oxygen delivery to the brain.

As yet CBF before and after venesection has not been compared

directly in primary and secondary polycythaemics. Accordingly we have measured CBF in patients with polycythaemia secondary to COAD before and after reduction of haematocrit and compared the results with those found in a group of primary polycythaemic patients. Comparisons of mean cerebral oxygen delivery, estimated by mean cerebral red cell flux (CRCF = CBF x haematocrit), have been made and the relationships of CBF and CRCF to haematocrit and blood viscosity have also been assessed in each group.

Our recent finding of apparent reversible suppression of the H-P-T axis in hypoxic male COAD patients has been considered due to reduced oxygen supply to the hypothalamus or pituitary[139,149] perhaps aggravated by the low cerebral blood flow of secondary polycythaemia. We therefore measured serum testosterone, FSH and LH in male patients in the secondary polycythaemic group before and after reduction of haematocrit.

PATIENTS

Four patients with primary polycythaemia (1 male, 3 female; age range 47-75, mean 66 years) and nine with polycythaemia secondary to chronic bronchitis (8 males, 1 female; age range 42-60, mean 52 years) were studied. Primary polycythaemia patients were obtained from a haematology clinic, the diagnosis of primary polycythaemia having been confirmed by blood volume studies and marrow histology. Secondary polycythaemics were obtained from a chest clinic and all had COAD using criteria previously described (Chapter I). Arterial blood gas estimations revealed that eight of the nine had arterial oxygen tensions of less than 7.4kPa (55mmHg) to account for the polycythaemia. One patient had a higher value (11.1kPa; 82mmHg) though he was a heavy cigarette smoker (>20/day) which itself can cause secondary polycythaemia[234]. All patients in the study had a venous haematocrit

between 0.55 and 0.70 (normal range 0.40-0.54). Red cell volume values ranged between 120-227 per cent (mean 170 per cent) of predicted normal[129].

Haematocrit was measured and blood viscosity was estimated in duplicate at both low ($0.94s^{-1}$) and high ($94s^{-1}$) shear rates. Reduction in haematocrit in all 13 subjects was achieved by venesections each of 500ml of blood at not less than weekly intervals till the haematocrit was less than 0.52. Cerebral blood flow was assessed before haematocrit reduction, halfway through the study in seven cases and again on completion. All repeat studies were performed at least one week after the previous venesection. The product of CBF and haematocrit yielded cerebral red cell flux. End-tidal carbon dioxide tensions were measured during CBF assessment.

Blood for hormone assay was taken from seven of the eight male secondary polycythaemic patients at 1100 hours at the start and finish of the study and serum levels of testosterone, LH and FSH were assessed. On completion of the study patients were asked whether overall they felt better, worse or no different.

RESULTS

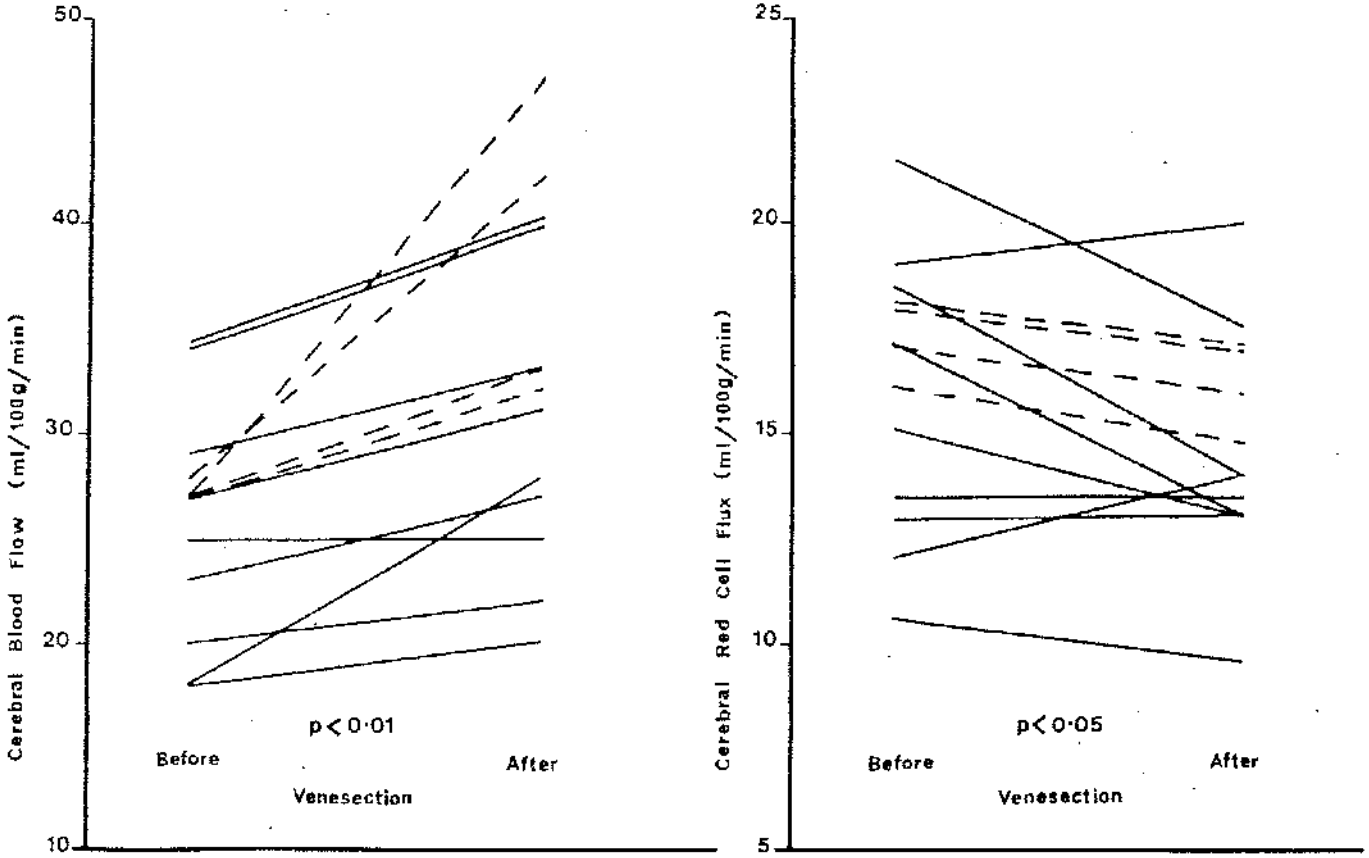
From table 26 it can be seen that at the commencement of the study mean levels of haematocrit, viscosity (at both low and high shear rates), CBF and CRCF were similar in the primary and secondary groups. End-tidal PCO_2 was significantly higher in the secondary group ($p<0.05$). Mean CBF was reduced well below our normal range (35-47, mean 41ml/100g/min) in both groups. In the combined group of 13 subjects, following reduction in haematocrit by venesections there was a significant fall in viscosity at both shear rates ($p<0.01$) and a significant rise in CBF (figure 20; $p<0.01$). After venesection of the four primary polycythaemic subjects mean

Changes in haematocrit, cerebral blood flow and other indices before and after venesection of primary and secondary polycythaemic patients (mean ± SEM)

		Primary Polycythaemia (n=4)	Secondary Polycythaemia (n=9)	Total (n=13)	
Haematocrit	-pre	0.636 ± 0.015	0.614 ± 0.018	0.621 ± 0.013	($p<0.01$)
	-post	0.425 ± 0.028	0.484 ± 0.020	0.466 ± 0.017	
Viscosity ($0.94s^{-1}$, mPa.s)	-pre	45.7 ± 5.6	44.9 ± 3.9	45.2 ± 3.1	($p<0.01$)
	-post	19.1 ± 4.1	24.8 ± 3.5	22.5 ± 2.7	
Viscosity ($94s^{-1}$, mPa.s)	-pre	9.23 ± 0.58	9.04 ± 0.44	9.12 ± 0.33	($p<0.01$)
	-post	5.42 ± 0.79	6.15 ± 0.61	5.86 ± 0.47	
pCO_2 (kPa)	-pre	4.71 ± 0.17	5.60 ± 0.37	5.33 ± 0.28	(N.S.)
	-post	4.73 ± 0.33	5.52 ± 0.32	5.28 ± 0.25	
CBF (ml/100g/min)	-pre	27.2 ± 0.2	25.4 ± 2.1	26.0 ± 1.4	($p<0.01$)
	-post	38.7 ± 3.7	29.5 ± 2.5	32.3 ± 2.3	
CRCF (ml/100g/min)	-pre	17.3 ± 0.4	15.5 ± 1.2	16.1 ± 0.9	($p<0.05$)
	-post	16.1 ± 0.6	14.1 ± 1.0	14.7 ± 0.7	

Viscosity = Whole blood viscosity; mPa.s = MilliPascal-second; pCO_2 = End-tidal carbon dioxide tension.
Statistics using Wilcoxon paired and unpaired tests.

Table 26



Cerebral blood flow and cerebral red cell flux at the start of the study and at the end after venesections in primary (— — —) and secondary (———) polycythaemia.

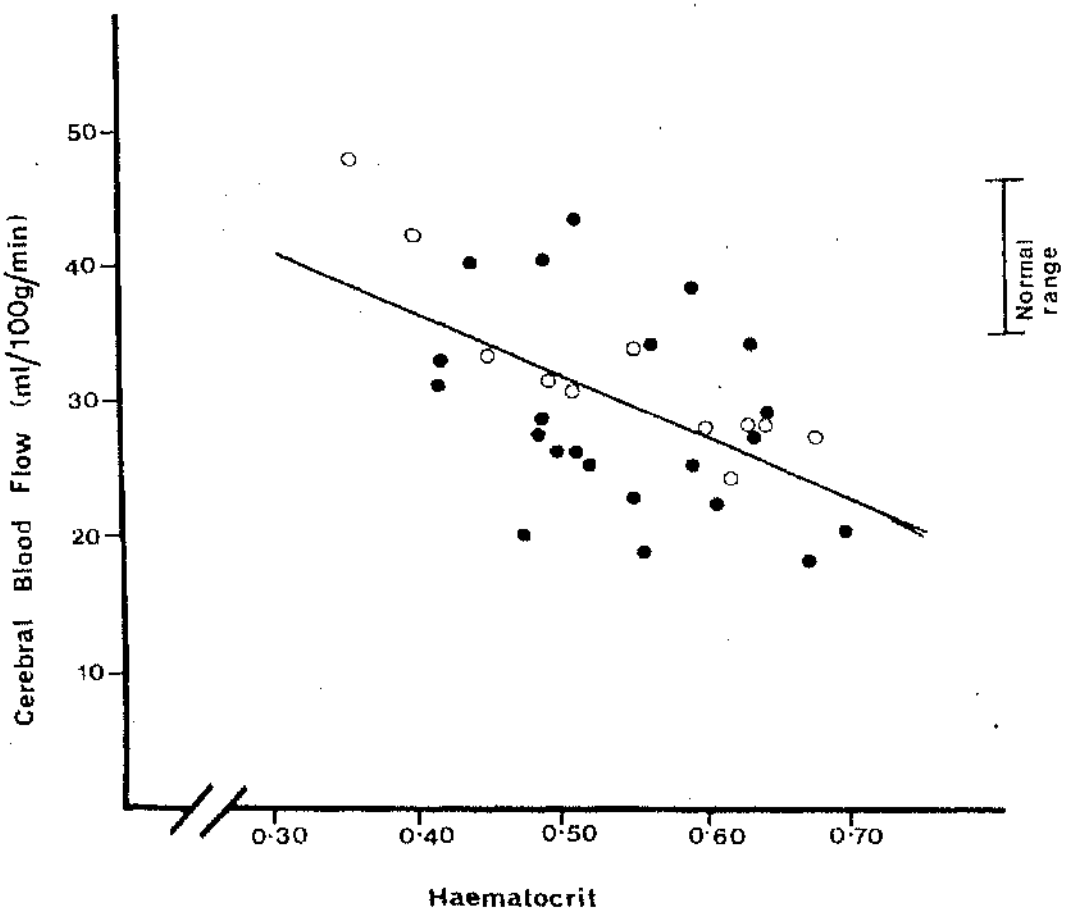
FIGURE 20

haematocrit fell by 33% and CBF rose by 41%. The mean fall in haematocrit in the secondary group was 21% and CBF rise 20%. The per cent rise in CBF for per cent fall in haematocrit was similar in each group. However with respect to oxygen delivery the rise in CBF after venesections in both groups was insufficient to compensate for the fall in haematocrit; after venesection CRCF (CBF x haematocrit), a measure of oxygen delivery, fell in 11 of the 13 patients (figure 20; $p<0.05$).

Figure 21 shows the relationship between CBF and haematocrit. As well as studies before commencement of and after completion of venesections in the 13 subjects, seven studies were performed during treatment, so a total of 33 studies was analysed. In the combined group the relationship was significant ($r = -0.57$, $p<0.001$). A close relationship was found when the primary group was considered separately ($r = -0.90$, $p<0.001$) but the correlation was poorer and not statistically significant in the secondary group ($r = -0.39$, $p>0.05$). The logarithm of blood viscosity at both shear rates showed a high correlation with haematocrit ($r = -0.93$, $p<0.001$) and hence with CBF ($r = -0.55$, $p<0.001$).

Of the seven secondary polycythaemic men in whom endocrine studies were made five had low or low normal serum testosterone and two had mid normal values before venesection. There were no consistent changes at completion of the study in serum testosterone levels or in serum LH or FSH levels (table 27).

Of the 13 patients nine felt symptomatically unchanged at the end of the study. Two secondary polycythaemic patients felt improved and two felt worse, one dying of respiratory failure two weeks after the haematocrit was reduced from 0.70 to 0.61: no autopsy was performed.



Correlation between cerebral blood flow and haematocrit in primary polycythaemic patients (O) and in those with polycythaemia secondary to COAD (●), r= 0·57, p< 0·001.

FIGURE 21

Changes in serum testosterone, LH and FSH before and after venesection with lowering of haematocrit in seven men with polycythaemia secondary to COAD

	Serum testosterone (nmol/l)		Serum LH (U/l)		Serum FSH (U/l)	
	Before	After	Before	After	Before	After
	9.9	14	9.8	22	6.6	13
	12	5.1	2.8	5.3	<0.9	1.6
	12	15	<2.3	2.3	1.6	1.6
	9.0	8.1	3.0	2.5	1.4	1.2
	10	7.2	<2.3	3.4	1.3	1.6
	17	17	<2.3	3.4	1.3	2.0
	24	27	5.3	2.8	1.6	<0.9
Mean	13.4	13.3	*		*	

* Mean values not calculable as low values are expressed as "less than" 2.3 for LH and "less than" 0.9 for FSH and not as absolute values.

Table 27

DISCUSSION

We confirmed decreased CBF in patients with primary polycythaemia[227]. We have also found a similar low level of CBF in patients with polycythaemia secondary to chronic bronchitis in contrast to a previous report of relatively normal CBF in secondary polycythaemics as compared with primary polycythaemics despite increased viscosity[230]. This discrepancy might be due to different methodology for CBF measurement or to a difference in mean PCO_2 which was higher in the previous study[230]. After venesection to reduce haematocrit and blood viscosity there was a significant rise in CBF in both groups as in previous reports[227,230]. However this study has compared the degree of CBF rise in each group and shown that the degree of increase in CBF per unit fall in haematocrit is similar in each group.

Two relevant questions are (a) what is the mechanism by which CBF is increased and (b) does this benefit patients? The factors which are said to increase CBF are hypercapnia, decreased oxygen content of the blood and lowering of blood viscosity. The fact that the higher level of PCO_2 in our secondary polycythaemic patients was not associated with a higher CBF at the start of the study suggests that chronic hypercapnia is not a major influence. The decrease in viscosity after venesection would seem a major influence in increasing CBF particularly in view of our finding of a close inverse relationship between viscosity and CBF. However a recent paper[235] demonstrated that after lowering plasma viscosity and thereby whole blood viscosity but leaving haematocrit unchanged, CBF did not increase and so it concluded that changes in CBF were mainly a physiological response to alterations in blood oxygen content brought about by fluctuations in haematocrit. However the degree of reduction in oxygen carrying capacity of the blood caused by lowering

of haematocrit is very small and so would seem unlikely to be the main influence[236]. In yet another recent publication[237] a correlation between both serum fibrinogen and haematocrit and decreased CBF suggested that viscosity factors are indeed important.

Symptomatic benefit from venesection in uncontrolled studies of patients with primary and secondary polycythaemia has been reported and ascribed to increased CBF[227,230]. However of our 13 patients two felt better (secondary group), nine felt no different and two felt worse (secondary group) after venesection, one of these dying of respiratory failure two weeks after his second venesection. Although mean CBF increased significantly after venesection, cerebral oxygen delivery in terms of cerebral red cell flux fell significantly because the fall in haematocrit outweighed the rise in CBF. These findings are similar to a previous study of venesection in secondary polycythaemia[230] which also showed a fall in mean cerebral oxygen carriage though in that series the degree of reduction did not achieve statistical significance. In view of reduced cerebral oxygen delivery after venesection in our secondary polycythaemic patients it is not surprising that serum testosterone, LH and FSH did not rise as we might have expected with improved oxygenation of the brain and pituitary. Venesection is of proven value in reducing vascular events and increasing survival in primary polycythaemia. Secondary polycythaemia patients seem less prone to such vascular events and the indications for lowering haematocrit are less well defined. Any symptomatic improvement in secondary polycythaemic patients, far from impressive in our patients, is apparently not due to increasing the amount of oxygen available to the brain. Our finding of reduced cerebral oxygen delivery suggests that caution with venesection is required in secondary polycythaemic patients, particularly those with

cerebral insufficiency. However there are other reasons for lowering haematocrit in these patients such as reducing pulmonary vascular resistance with a consequent improvement in work capacity[232].

In conclusion then this study has demonstrated that contrary to earlier work CBF is reduced to a similar degree in secondary as in primary polycythaemia. It is the first study to compare the changes in CBF after venesection in the two groups and to show that the increase in both instances is proportional to the percentage fall in haematocrit. Our findings suggest that viscosity is a major influence on CBF but the field remains open for further investigation. Despite increased CBF, cerebral oxygen delivery falls after venesection and so the benefits in secondary polycythaemia may be restricted to reducing pulmonary vascular resistance and so relieving resistant cor pulmonale failure.

CHAPTER XV

EFFECT OF OXYGEN THERAPY ON ENDOCRINE FUNCTION IN MEN WITH HYPOXIC PULMONARY DISEASE[238]

Four stable but hypoxic men with COAD and one with pulmonary fibrosis showed improvement in depressed serum testosterone levels after continuous oxygen therapy. Pituitary stress tests where low also tended to improve thus adding further supportive evidence that such suppression of the H-P-Testicular axis is hypoxic in origin.

INTRODUCTION

In earlier studies we have shown that the H-P-Testicular axis is suppressed in the hypoxic stages of chronic obstructive airways disease (Chapters V and VII)[139,149] and pulmonary fibrosis (restrictive lung disease) (Chapter IX)[160]. In view of a significant correlation between PaO_2 and serum testosterone values in both conditions (Chapters VI and IX)[148,160] it seemed possible that hypoxia itself was the suppressant factor. In COAD patients we found that an increase in PaO_2 with recovery from acute phase cor pulmonale was associated with enhanced testosterone production (Chapter VIII)[156] while a fall in PaO_2 in deteriorating pulmonary fibrosis patients was accompanied by a reduction in testosterone output (Chapter IX)[159,160]. These findings in addition to the known reduction in urinary 17-ketosteroid production in visitors to high altitude[82,97,100,112] lend further support to the theory of a causal relationship between hypoxia and H-P-Testicular suppression. These observations led us to conclude that a trial of oxygen therapy in hypoxic respiratory patients was indicated to determine whether by increasing levels of PaO_2 artificially the H-P-Testicular axis depression might be reversed.

PATIENTS AND METHODS

Eight male patients with COAD who were either outpatients or previously had been admitted to hospital with an exacerbation, had been identified as possible suitable candidates for the study. Criteria of COAD were as described previously (Chapter I) and all at this stage were hypoxic with low or low-normal serum testosterone values. However by the time of study two had recovered so well that they were no longer hypoxic while two others were found to have mid-normal serum testosterone levels despite significant hypoxia (PaO_2 7.5 and 5.5kPa; 56 and 41mmHg) so all four were excluded. Of the four remaining (table 28, Nos 1-4) all were hypoxic (range 5.1-7.2kPa; 38-54mmHg) and had low or low-normal serum testosterone values. One additional male patient with pulmonary fibrosis diagnosed using similar criteria to those patients in Chapter IX[160] was included. His initial PaO_2 was 8.9kPa (67mmHg) and serum testosterone was low-normal (12nmol/l). After four months with gradual clinical deterioration PaO_2 had fallen to 6.4kPa (48mmHg), serum testosterone was frankly low (4.8nmol/l) and he was studied at this stage (table 28, No 5).

Study patients were admitted to hospital and had arterial blood gas estimations on two consecutive days breathing room air at rest as previously described. Following the second of these estimations blood was taken for hormone analysis and a pituitary stress test was performed as before (Chapter I). Following this oxygen therapy was commenced using nasal prongs and an oxygen flow of between 2-4l/minute. Blood gases were repeated while on oxygen, the flow being tailored to produce a substantial increase in PaO_2 without inducing significant hypercapnia. Confined to bed on a no smoking regime (three were current cigarette smokers) they were encouraged to receive oxygen

Clinical details, drug histories and effects of oxygen therapy on arterial blood gases in stable hypoxic male respiratory patients

	Patient	Age (yr)	Diagnosis	Days of O_2 therapy	PaO_2 (kPa)	$PaCO_2$ (kPa)	pH	Base excess (mmol/l)	Cigarettes	Drugs
Before O_2 Therapy	1	61	COAD	0	5.1	7.9	7.39	+8	Ex smoker for 5 years	Salbutamol, aminophylline, digoxin, frusemide
After				5	7.6 (8.4 = mean of 4 PaO_2 values on O_2 therapy)	7.7	7.39	+7		No change
Before O_2 Therapy	2	66	COAD	0	6.0	6.3	7.47	+8	10/day	Salbutamol, frusemide, spironolactone
After				18	7.6 (9.1 = mean of 4 PaO_2 values on O_2 therapy)	6.0	7.41	+3		No change
Before O_2 Therapy	3	41	COAD	0	6.7	6.1	7.35	-1	40/day	Salbutamol
After				18	8.5 (8.7 = mean of 4 PaO_2 values on O_2 therapy)	5.7	7.31	+3		Salbutamol, ampicillin
Before O_2 Therapy	4	51	COAD	0	7.2	8.0	7.33	+3	20/day	Nil
After				18	10.9 (10.1 = mean of 4 PaO_2 values on O_2 therapy)	8.4	7.34	+5		Nil
Before O_2 Therapy	5	68	Idiopathic pulmonary fibrosis	0	6.4	4.4	7.49	+3	Ex smoker for 1 year	Frusemide, prednisolone, lactulose
After				14	10.7 (10.5 = mean of 4 PaO_2 values on O_2 therapy)	5.7	7.44	+4		No change
Normal Range					10.7-13.3	4.7-6.0	7.36-7.44	±3		

Table 28

therapy for at least 20 hours each day and were permitted to remove nasal prongs for toilet visits only. Patient No 1 received oxygen for five days and Nos 2-5 received it for approximately two weeks. During the study, they remained on their preadmission drug therapy (table 28). Just before discontinuing the oxygen therapy endocrine studies were again performed. All the hormone blood sample levels were assayed as described in Chapter I.

RESULTS

A substantial increase in PaO_2 on oxygen therapy was achieved in each patient. PaO_2 increased by an average of 3.3kPa; 25mmHg and in each case the mean PaO_2 during treatment exceeded 8.0kPa; 60mmHg. This was achieved in each case without significantly elevating $PaCO_2$ (table 28). Patient No 3 developed a chest infection associated with pyrexia and purulent sputum and received ampicillin for seven days during the study but otherwise there were no alterations in drug therapy.

Serum testosterone values rose in all patients, per cent increases over basal values in patients 1-5 being 62,6,218,15 and 42 respectively (table 29). There were no major changes in SHBG values but these were mildly elevated in patients 2,3 and 4. Normal serum T_3 and T_4 rose after oxygen therapy in the four COAD patients. Serum androstenedione level was low in patient No 5 and serum DHAS levels were low in patients 1,2,4 and 5 but these did not change appreciably with oxygen therapy.

Serum LH response to injected GnRH was low in patient No 1 and improved after oxygen therapy (table 30). Serum FSH responses to GnRH were low in patients 1 and 2 and improved in both after oxygen therapy. TSH responses to injected TRH were low in patients 2,4 and 5

Effect of oxygen therapy on various serum hormone levels in stable hypoxic male respiratory patients

	Patient	17 OHA (testosterone) (nmol/l)	SHBG (nmol/l)	T_3 (nmol/l)	T_4 (nmol/l)	Androstenedione (nmol/l)	DHAS (μmol/l)
Before		3.9	30	1.2	115	4.3	1.2
O_2 Therapy	1						
After		6.3	32	1.3	122	2.9	<1.0
Before		7.2	48	1.1	71	3.2	1.4
O_2 Therapy	2						
After		7.6	50	1.9	104	4.6	1.6
Before		4.4	46	1.6	91	5.1	8.9
O_2 Therapy	3						
After		14	54	2.4	97	3.2	7.9
Before		13	58	1.8	78	2.4	1.5
O_2 Therapy	4						
After		15	43	2.2	89	2.0	2.1
Before		4.8	43	1.3	99	1.5	<1.0
O_2 Therapy	5						
After		6.8	44	0.8	68	1.5	<1.0
Normal Range		11-36	5-45	0.9-2.8	55-144	2-11	2-9

Table 29

Effect of oxygen therapy on gonadotrophin responses to injected GnRH and TSH and prolactin responses to injected TRH in stable hypoxic male respiratory patients

	Patient	Serum LH response (U/l)			Serum FSH response (U/l)			Serum TSH response (mU/l)			Serum Prolactin response (mU/l)		
		0'	30'	60'	0'	30'	60'	0'	30'	60'	0'	30'	60'
Before		4.0	11	15	<1.0	<1.0	<1.0	2.1	6.5	7.4	66	370	140
O_2 Therapy	1												
After		4.7	14	19	<1.0	2.0	2.8	1.0	4.9	3.1	63	770	370
Before		8.6	20	22	3.4	3.8	3.0	1.0	1.6	1.1	150	460	350
O_2 Therapy	2												
After		13	21	20	5.6	6.8	6.6	1.0	2.3	1.5	220	480	320
Before		6.9	29	28	3.7	10	10	1.0	5.4	3.7	60	200	130
O_2 Therapy	3												
After		4.6	38	39	4.0	6.7	6.2	1.5	6.7	6.2	90	520	350
Before		20	61	52	28	>40	>40	1.1	4.2	4.1	280	760	580
O_2 Therapy	4												
After		22	77	76	22	>40	>40	1.8	8.3	6.6	290	820	690
Before		11	42	26	5.2	10	8.0	<1.0	3.1	1.2	150	1200	670
O_2 Therapy	5												
After		13	36	43	9.6	14	16	<1.0	2.5	1.8	160	1400	1200
Normal Range		UD-9.0	20-42	20-38	UD-7.0	4-18	4.5-21	UD-8.0	Increment>3.6 (30'>60')		60-360	Increment>65% of basal (30'>60')	

UD = Undetectable

Table 30

and improved with oxygen therapy in patients 2 and 4. Basal prolactin levels and responses to TRH were normal throughout.

DISCUSSION

This definitive experiment to test whether hypoxia itself suppressed the H-P-Testicular axis has proved more difficult to execute than we had imagined. At the outset we appreciated that the hypothesis would be impossible to prove absolutely because of other variable and possibly relevant aspects of the trial regime. Admission to hospital, itself a change in environment, required bed rest during the study because of the continuous use of oxygen nasal prongs. There were few opportunities for clandestine smoking and a change in this habit might influence results as cessation of cigarette smoking has been shown to be associated with slight increase in testosterone levels[158].

Considering requirements of the study we encountered a number of problems in their execution. Each patient during the study though hypoxic had to be in a stable clinical state with as few as possible changes in habit and drug therapy. However clinically stable COAD patients tend not to be profoundly hypoxic and several candidates selected as potentially suitable during treatment in hospital had to be rejected from the study when they were found at follow-up to have near normal PaO_2 levels. Then again hypoxic COAD patients tend to have hypercapnia and while this study required the PaO_2 to rise appreciably this was sometimes not possible without inducing significant hypercapnia and respiratory depression. A further problem encountered was compliance with oxygen self administration. Though instructed not to smoke and to take oxygen day and night, only removing nasal prongs for toilet visits, they were often

reported by nursing staff not to be taking oxygen and sometimes smoking clandestinely. These problems of compliance[239] and of continuing to smoke while receiving oxygen therapy[240] have been encountered by other workers.

While selecting patients for this study we came across patient No 5 with pulmonary fibrosis whose PaO_2 level had deteriorated along with a fall in serum testosterone level. This was very similar to two other cases in our study of pulmonary fibrosis (Chapter IX)[159] and helped to confirm our impression that sex hormone status can fluctuate with lung disease severity. We also encountered two hypoxic COAD patients with normal serum testosterone levels, reminding us that such hormone suppression is not an invariable accompaniment of hypoxia. Indeed we have already shown that in COAD, 20 per cent of patients with PaO_2 values less than 6.6kPa (50mmHg) have normal serum testosterone levels (Chapter VI, figure 8)[148].

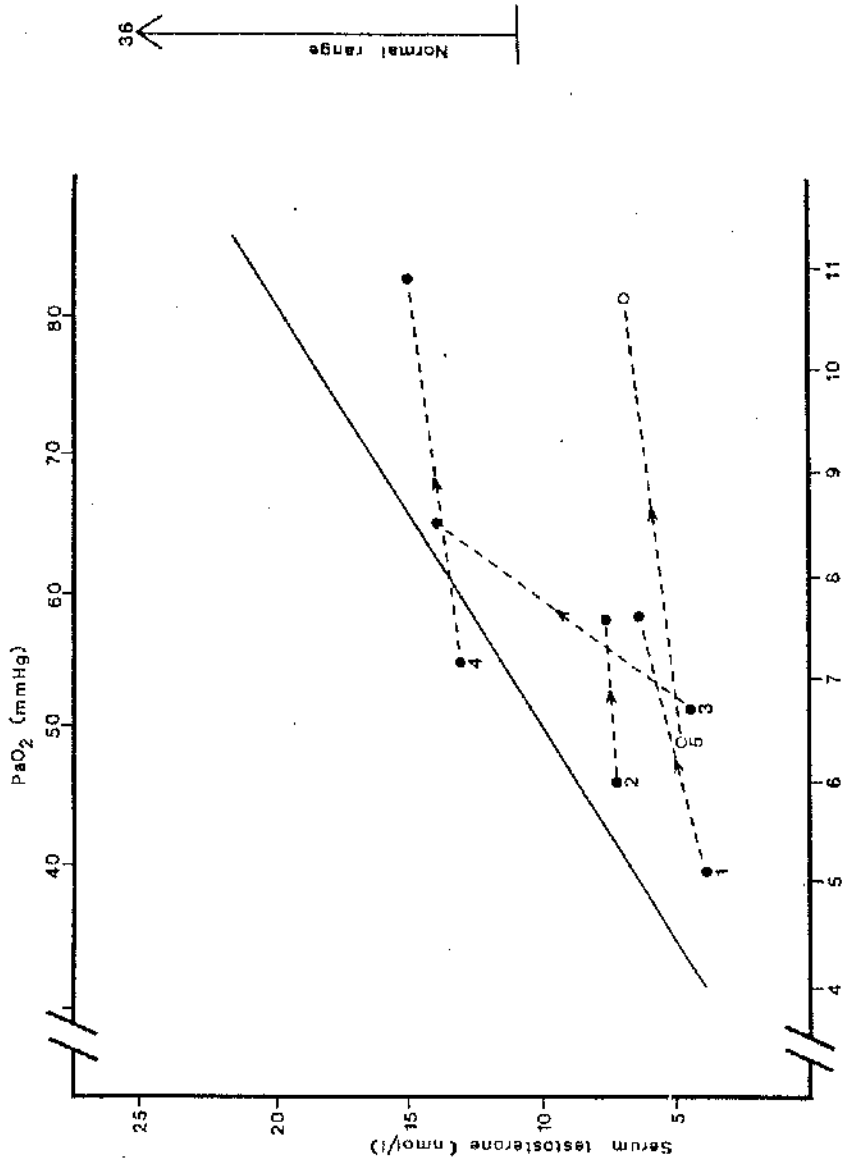
Serum testosterone rose in all patients during oxygen therapy, though only modestly in patients 2 and 4 (table 29). With the exception of patient No 1 initial low testosterone values were not associated with poor LH response to injected GnRH and thus were probably a result of hypothalamic suppression (table 30). Our previous studies of COAD patients (Chapter VII, figure 12)[149] also suggested hypothalamic suppression to be responsible for the deficient steroidogenesis whereas in some pulmonary fibrosis patients (Chapter IX, table 14)[159] the disturbance seemed more likely to be at pituitary level. However a recent article[241] has stated that "early hopes that the use of the hypothalamic peptides TRH and GnRH might reliably separate intrinsic pituitary failure from failure of hypothalamic origin have foundered". It appears that a single dose GnRH stimulation test may yield the same reponse from a small

fraction of still functioning pituitary as it does from an intact gland inactive because of longstanding undersecretion of natural GnRH by an underactive hypothalamus. It appears then, as we postulated in Chapter IX that low testosterone in hypoxic lung disease may be due to hypothalamic suppression despite apparent pituitary failure in some cases.

FSH responses to injected GnRH were low in two COAD patients (table 30) and this was also the case in our earlier study (Chapter VII, figure 13)[149]. Diminished TSH responses to injected TRH occurred in three of the five patients in this study and it will be recalled that similar evidence of apparent pituitary suppression was found in two of eight COAD patients (Chapter VII, table 12)[149] and in two of eight pulmonary fibrosis patients (Chapter IX, table 15)[160]. Serum T_3 and T_4 values were normal but interestingly the four COAD patients, but not the pulmonary fibrosis case, showed increases in both hormones with improved oxygenation. From table 30 it can be seen that where LH or FSH responses to injected GnRH were low before oxygen therapy they improved during treatment. This was true also of two of the three patients with poor TSH responses to injected TRH.

The androgen androstenedione which was shown to be low in two of seven COAD patients in acute phase cor pulmonale and which tended to increase with recovery (Chapter VIII, figure 16)[156] was normal in the four COAD patients in this study. DHAS already shown to be low in acute phase cor pulmonale and to increase with recovery was low in four of the five patients in this study, but there was no improvement after oxygen therapy. Normal prolactin values throughout confirms our earlier impression that prolactin status is usually unchanged in such patients.

Figure 22 shows the increase in serum testosterone plotted against



Serum testosterone levels before and after oxygen therapy in four hypoxic patients with COAD (●) and one with pulmonary fibrosis (○).
(——— = regression line showing correlation between PaO_2 and serum testosterone in previous COAD patients – see figure 8)

FIGURE 22

increase in PaO_2 associated with oxygen therapy in the five patients. The average increase in serum testosterone was 1.2nmol/l per 1kPa increase in PaO_2. This compares with an average change in serum testosterone of 2.4nmol/l per 1kPa change in PaO_2 for our previous COAD patients according to the regression line of figure 8 which is also included in figure 22. Thus the anticipated degree of increase in serum testosterone was not achieved with the oxygen therapy. This could be explained either by poor oxygen compliance during the study, by the small number of patients involved or perhaps by inadequate duration of oxygen therapy.

Despite the limitations of this study we believe that the modest yet invariable increase in serum testosterone levels and improvement in pituitary stress test results accompanying continuous oxygen therapy provides further evidence of hypoxic suppression of the hypothalamo-pituitary-testicular axis.

CHAPTER XVI

CONCLUSIONS

It has long been recognised that men with chronic obstructive airways disease tend to conform to one of two distinct patterns, distinguished pathologically by a differing distribution of emphysema in relation to the pulmonary acinus and clinically by contrasting physical appearances. As yet the reasons for these differences have seldom been investigated and are little understood but it has been suggested that genetic factors may be responsible. In alpha-1-antitrypsin deficient subjects with hereditary panacinar emphysema we found, as we did in other types of emphysema, that weight loss is a frequent accompaniment of clinical respiratory deterioration. It seems possible that other genetic factors may contribute to the development of emphysema. The thin endomorph, sometimes with features not unlike Marfan's syndrome is more susceptible to 'idiopathic' spontaneous pneumothorax which has been related to thin visceral pleura with blebs which are prone to rupture. Perhaps similar mesodermal factors may in some way dictate the panacinar type of emphysema found in this build of man after years of smoking. It can be said now that neither dietary intake nor malabsorption is a likely cause of weight loss in these pink puffers. Although they appear to work harder in breathing than do blue bloaters, such added energy expenditure is relatively small and therefore probably unimportant as a contribution to weight loss.

Endocrine abnormalities noted for the first time in these studies may contribute in some way to these extremes of body habitus but it must be said that the hormone changes in the two groups tend to show as many similarities as they do contrasts. Testosterone output is low in both groups, apparently due to hypoxic suppression of the

hypothalamus and this is reversible with recovery from acute phase cor pulmonale and with oxygen therapy. It causes organic sexual impotence, may contribute to osteoporosis and is perhaps related to the obesity of the blue bloater. The absence of fat in the pink puffer could be due to counteraction of this low testosterone effect by the adrenal androgen DHAS present at high level in these patients.

Despite our contention that hypoxia can affect the hypothalamo-pituitary-testicular axis by depressing the hypothalamus in both COAD and pulmonary fibrosis, we have evidence that the hypothalamo-pituitary-adrenal and hypothalamo-pituitary-thyroid axes in both conditions are relatively spared. The fact that the H-P-Testicular axis was well preserved in our severely hypoxic men with cyanotic congenital heart disease may be explained by their life-long tolerance to hypoxia. Nevertheless it would be of interest to compare endocrine function during sleep stages in both types of patient to determine whether the respective hormone patterns are associated with their previously identified differences in arterial oxygen saturation during REM sleep.

Our metabolic studies, using techniques other than isotope dilution, suggest that lean body mass continues to fall after recovery from acute phase cor pulmonale yet we and previous workers, measuring intracellular water by isotope dilution and thereby estimating lean body mass, showed an apparent increase under similar circumstances. Our conclusion is that isotope water techniques can be unreliable in cor pulmonale and this has important implications for future metabolic and isotope dilution studies in hypoxic clinical conditions. For the first time using a whole body monitor, total body potassium values have been shown to be low in COAD. Neither diuretic therapy nor loss of lean body mass seem to be solely responsible and other factors will

have to be considered.

Our study in secondary polycythaemic COAD patients demonstrated for the first time that cerebral blood flow (CBF) is reduced to a similar degree in secondary as in primary polycythaemics. We have confirmed that such polycythaemia is a usual accompaniment of hypoxia in COAD, so reduced CBF is probably a common phenomenon in this condition. Our studies suggest that such reduced CBF is not causally related to the endocrine abnormalities.

Several of these findings have therapeutic implications. Oxygen replacement therapy as commonly practised in acute phase cor pulmonale seems entirely logical though compliance problems and expense with long term domiciliary oxygen therapy may limit its use. Diuretic therapy may not be appropriate in all instances of acute phase cor pulmonale as there is probably little net retention of fluid and as it may further increase the potassium loss. Digoxin is notoriously unhelpful in these cases, due perhaps in part to the low TBK and also because the fluid shift tends to be cellular rather than vascular in origin. It seems from our CBF findings that venesection should be performed only in specially selected secondary polycythaemic patients as a proportion may deteriorate following the procedure.

There are several "follow on" problems awaiting our attention. As yet we have not studied the benefits of potassium or testosterone replacement therapy and in particular what effect the latter has on libido, sexual performance and body habitus. We should look again at DHAS in pink puffers and blue bloaters to determine whether there is indeed a marked difference in production of this hormone which might contribute to the differences in body habitus. A search should be made in hypoxic COAD patients with low androgen production for generalised osteoporosis which might be improved by testosterone

replacement therapy. In due course an opportunity may be found to investigate female patients with COAD.

The studies included in this thesis and the writing of associated papers have preoccupied the author helped by various colleagues during the last nine years. For us the most exciting discovery has been the finding of testosterone depression in these hypoxic men with all its possible implications not least its future role in antismoking education. It seems to us that this association may well be the most common cause of organic sexual impotence always previously considered to be infrequently caused by sex hormone upset. It seems remarkable that these endocrine aspects of COAD, a very common condition, have been unrecognised or ignored by past workers and it has surprised us also that so far none have attempted to confirm or refute our findings.

We are involved in planning further studies at this stage and as the field is so vast and relatively unexplored anticipate being fruitfully involved in the years to come.

APPENDIX

HYPOXIA, TESTOSTERONE DEPRESSION AND SEXUAL IMPOTENCE IN PICKWICKIAN SYNDROME REVERSED WITH WEIGHT REDUCTION[242]

Weight reduction in an obese man with Pickwickian syndrome produced improvement in pulmonary function and oxygenation along with an increase in production of various hormones. Significant correlations between PaO_2 and serum testosterone, FSH, DHAS, T_3 and T_4 suggested a causal relationship. Symptomatic improvement included a return of normal sexual function.

INTRODUCTION

During our studies in hypoxic COAD (chapters V-VIII)[139,148,149,156], pulmonary fibrosis (chapter IX)[159,160] and cyanotic congenital heart disease (chapter X)[168] it was apparent that suppression of the hypothalamo-pituitary-testicular axis and associated sexual impotence (chapter XI) was present in both respiratory conditions but not in CCHD despite a similar degree of hypoxia. Postulated reasons for the differences (chapter X) were that the CCHD patients had become acclimatised to hypoxia from an early age and that profound hypoxia of REM sleep which occurs in COAD and pulmonary fibrosis but not in CCHD might be the suppressant factor. Such hypoxic dips also occur during REM sleep in obstructive sleep apnoea (Pickwickian) syndrome patients[169,243] but there have been few investigations of sex hormone status in such individuals despite the finding that as many as 42 per cent are sexually impotent[243]. Recently we were fortunate to have the opportunity to study a typical and florid example of the syndrome.

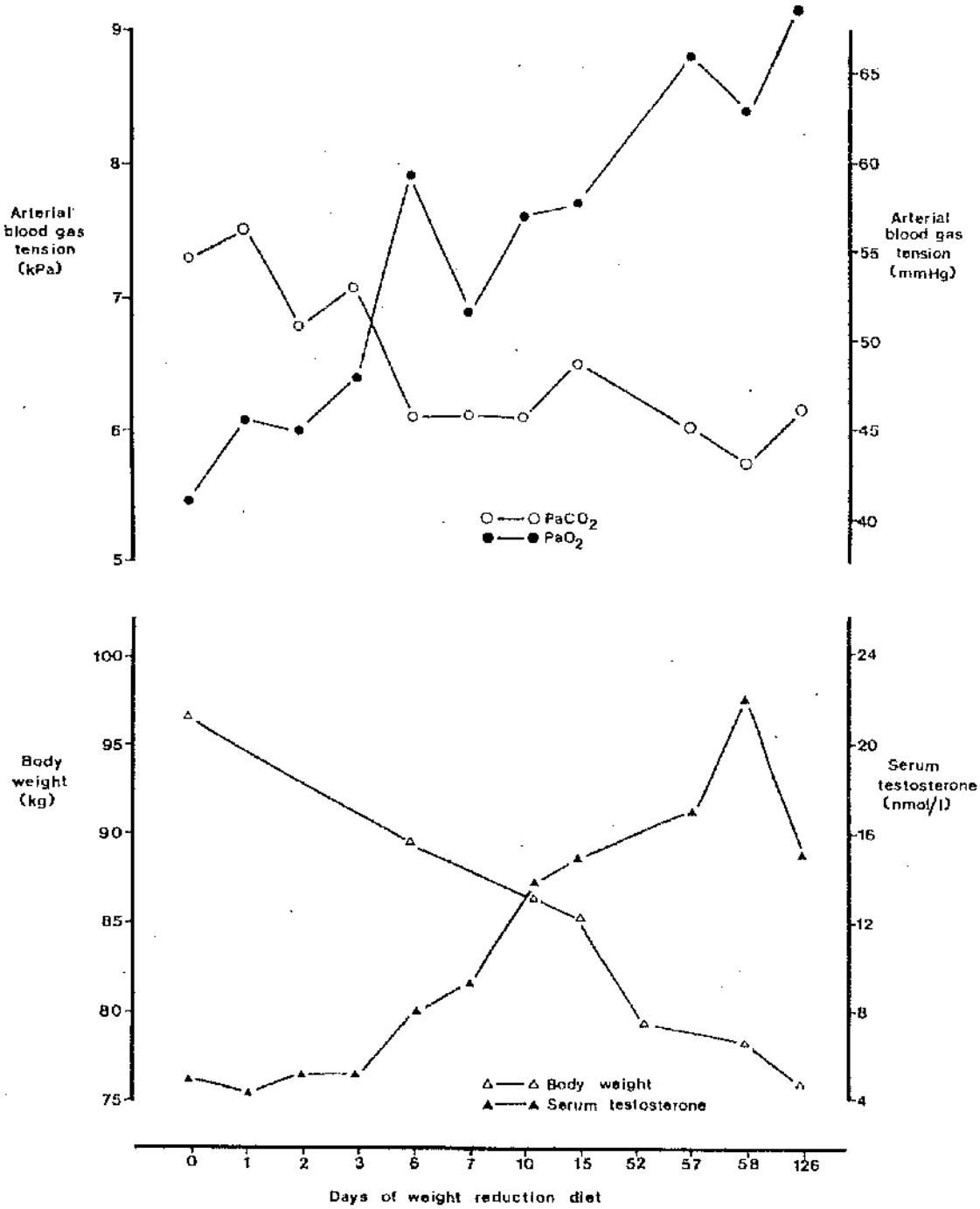
CASE REPORT

A 58 year old man with no previous illness and on no drugs presented with a six month history of daytime somnolence and inability

to concentrate which had developed during rapid weight gain of 20kg following discontinuation of smoking nine months previously. Snoring had become accentuated and whereas sexual intercourse used to occur approximately twice weekly he had been impotent with no intercourse or early morning penile erections for six months. He was short necked and cyanosed with elevated jugular venous pulse and was admitted for investigations and weight reduction.

Methods - Investigations were performed initially (day 0) and at intervals during 126 days of weight reduction diet (figure 23). Methods for hormone assays were as previously described (chapter I) with the addition of free testosterone calculated by the method of Lawrence and colleagues[244], serum thyroxine binding globulin using the Corning Immunophase kit and serum free thyroxine using an analogue binding method (Amerlex; Amersham International). Correlations between PaO_2 and various hormones were tested by a least sum of squares linear fit.

Results - With weight reduction there was a commensurate rise in PaO_2 from subnormal levels and fall in $PaCO_2$ from hypercapnic levels (figure 23, table 31). Both dynamic and static lung volumes increased with weight loss (table 32). Serum testosterone rose from subnormal to normal levels within 10 days (figure 23, table 33). Sex hormone binding globulin was normal at the start of the study and rose during it (figure 24, table 33). Free testosterone index and calculated free testosterone rose from subnormal values at the start to normal values at the end (figure 24, table 33). Serum dehydroepiandrosterone sulphate (DHAS), though normal at the start, tended to rise during the study (table 33). Androstenedione remained normal and unchanged throughout. Serum T_3 and T_4 values though normal throughout tended to increase during the study (figure 25, table 33). Basal serum LH was normal and remained unchanged (table 31). Basal serum FSH was normal and tended to rise during the study. Basal TSH levels were low-normal throughout



Sequential measurements of body weight, serum testosterone and arterial oxygen and carbon dioxide tensions in a man with obstructive sleep apnoea (Pickwickian) syndrome during weight reduction diet.

FIGURE 23

Sequential measurements of body weight, arterial blood gas measurements and various pituitary hormone values in a man with obstructive sleep apnoea (Pickwickian) syndrome before (day 0) and after weight reduction diet

Day	Body weight (kg)	PaO_2 (kPa)	$PaCO_2$ (kPa)	pH	Base excess (mmol/l)	LH (U/l)	FSH (U/l)	TSH (mU/l)	Prolactin (mU/l)
0	96.5	5.5	7.3	7.40	+6	5.0	2.6	<1.0	110
1	ND	6.1	7.5	7.38	+6	ND	ND	ND	ND
2	ND	6.0	6.8	7.40	+5	8.7	3.0	<1.0	160
3	ND	6.4	7.1	7.39	+5	6.4	3.0	<1.0	140
6	89.5	7.9	6.1	7.37	0	4.9	3.4	<1.0	260
7	ND	6.9	6.1	7.39	+2	4.9	3.2	<1.0	170
10	86.5	7.6	6.1	7.39	+2	9.0	6.0	<1.0	130
15	85.2	7.7	6.5	7.36	+1	5.8	7.2	<1.0	150
52	79.2	ND	ND	ND	ND	ND	ND	ND	ND
57	78.7	8.8	6.0	7.41	+3	5.8	7.2	<1.0	150
58	ND	8.4	5.7	7.40	+2	ND	ND	ND	ND
126	76.0	9.2	6.1	7.39	+2	4.5	5.0	<1.0	60
Normal range	67(=ideal)	10.7-13.3	4.7-6.0	7.36-7.44	±3	UD-9.0	UD-7.0	UD-8.0	60-360

Table 31

Measurement of pulmonary function in a man with obstructive sleep apnoea (Pickwickian) syndrome near the start of and at intervals during weight reduction diet

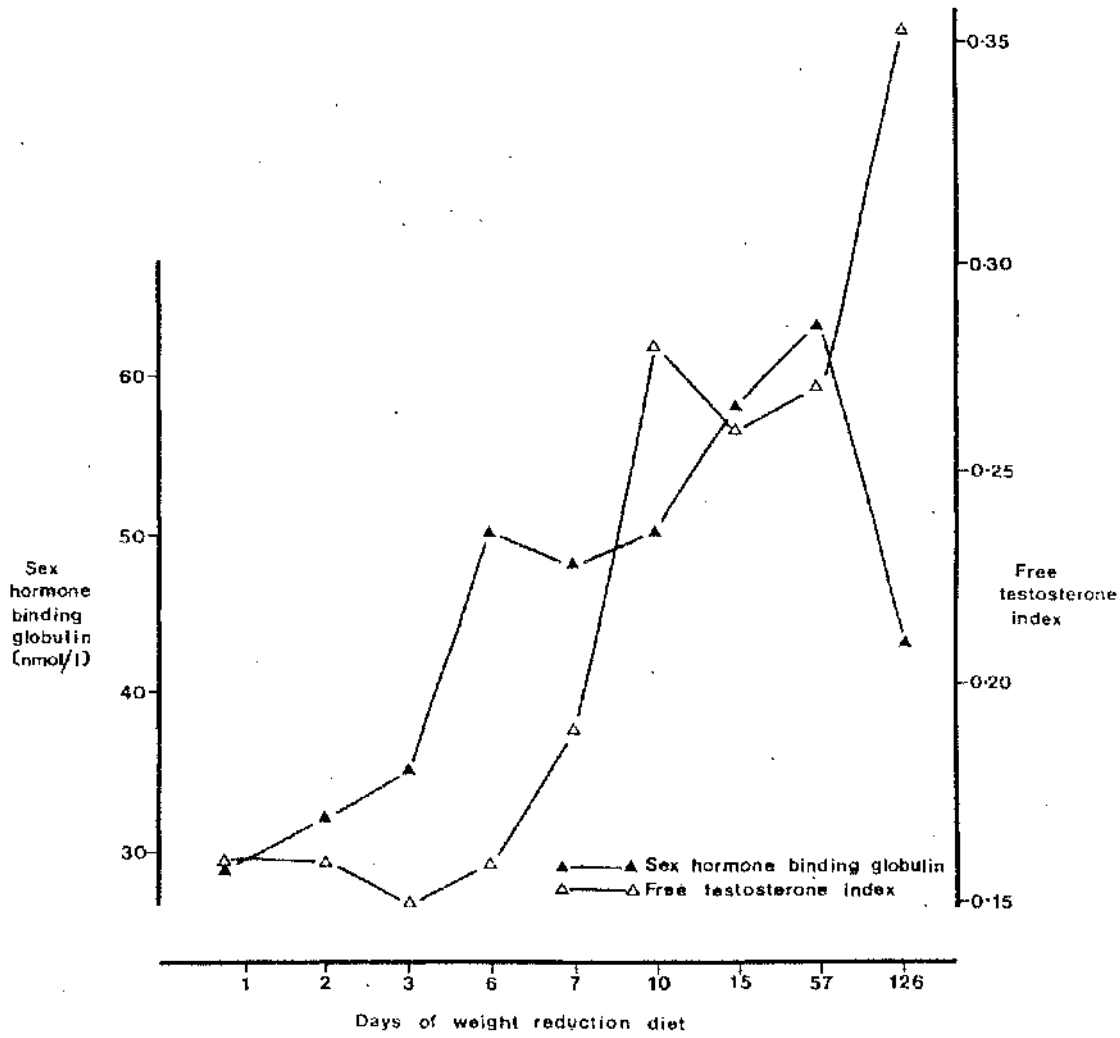
Day	Body weight (kg)	PEFR (l/min)	FEV_1 (l/sec)	FVC (l)	FEV_1/FVC (%)	TLC (l)	RV (l)	TF (mmol/min/kPa)
0	96.5	250	1.20	1.85	65	ND	ND	ND
9	87.0	ND	1.70	2.65	64	4.64	1.99	10
72	77.0	ND	2.15	3.15	68	5.94	2.79	9
126	76.0	430	ND	ND	ND	ND	ND	ND
Predicted normal	67(=ideal)	560	2.6	3.4	68	5.5	2.0	7

Table 32

Sequential serum measurements of various androgens and thyroid hormones in a man with obstructive sleep apnoea (Pickwickian) syndrome before (day 0) and after weight reduction diet

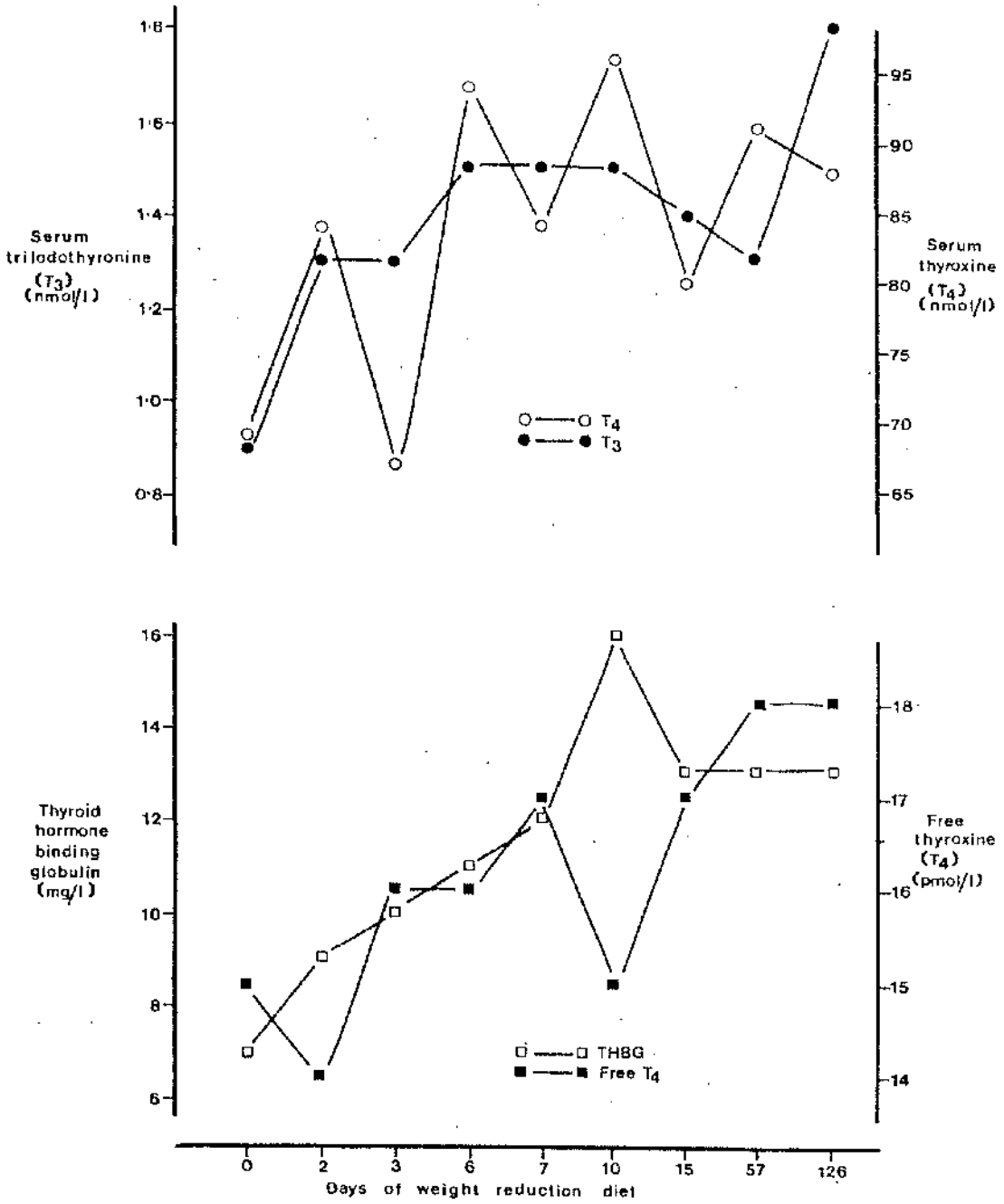
Day	Testosterone (nmol/l)	SHBG (nmol/l)	Free testosterone index	Calculated free testosterone (pmol/l)	DHAS (μmol/l)	Androstenedione (nmol/l)	T_3 (nmol/l)	T_4 (nmol/l)	Free T_4 (pmol/l)	Thyroid binding globulin (mg/l)
0	4.9	29	0.16	80	3.5	4.6	0.9	69	15	7
1	4.3	ND	ND	ND	ND	ND	ND	ND	ND	ND
2	5.1	32	0.16	81	3.7	4.8	1.3	84	14	9
3	5.1	35	0.15	78	3.9	3.2	1.3	67	16	10
6	8.0	50	0.16	100	4.5	4.9	1.5	94	16	11
7	9.2	48	0.19	120	4.8	3.7	1.5	84	17	12
10	14	50	0.28	180	3.4	4.2	1.5	96	15	16
15	15	58	0.26	180	3.7	4.2	1.4	80	17	13
57	17	63	0.27	200	8.7	3.7	1.3	91	18	13
58	22	ND	ND	ND	ND	ND	ND	ND	ND	ND
126	15	43	0.34	210	7.4	2.9	1.8	88	18	13
Normal range	11-36	5-45	0.3-1.8	200-600	2-9	2-11	0.9-2.8	55-144	9-25	12-30

Table 33



Sequential measurements of sex hormone binding globulin and free testosterone index in a man with obstructive sleep apnoea (Pickwickian) syndrome during weight reduction diet.

FIGURE 24



Sequential measurements of serum thyroxine, triiodothyronine, thyroid binding globulin and free thyroxine in a man with obstructive sleep apnoea (Pickwickian) syndrome during weight reduction diet.

FIGURE 25

and basal prolactin was normal and remained unchanged. Serum LH and FSH responses to injected GnRH were normal at the start and end of the study (table 34). Serum TSH responses to injected TRH were absent till the last occasion tested (day 126) when they were normal. Serum prolactin responses were normal throughout.

Correlations between PaO_2 and various hormones were as follows: serum testosterone - $r=0.843, p<0.01$: SHBG - $r=0.747, p<0.05$: free testosterone index - $r=0.813, p<0.01$: calculated free testosterone - $r=0.866, p<0.01$: LH - $r=-0.281$,NS: FSH - $r=0.703, p<0.05$: DHAS - $r=0.757$, $p<0.05$: androstenedione - $r=-0.045$,NS: T_3 - $r=0.741, p<0.05$: T_4 - $r=0.670, p<0.05$: thyroid binding globulin - $r=0.730, p<0.05$: free thyroxine - $r=0.781, p<0.05$.

DISCUSSION

The presenting clinical features of this patient are quite typical of obstructive sleep apnoea syndrome as described by previous authors[243,245,246]. The improvement in lung volumes is that expected with weight reduction in this condition[247] as well as the return to normal of arterial blood gas tensions[247,248]. Indeed the latter has been achieved in certain cases by relieving upper airways obstruction by tracheostomy or other surgical procedure with consequent improvement of sexual function[249]. To date endocrine studies before and after dietary or surgical treatment of these impotent subjects have not been reported. However Mosko and colleagues[250] did describe delayed sexual maturation in a 20 year old male with obstructive sleep apnoea syndrome associated with enlarged tonsils and adenoids. LH production fell dramatically during sleep and was associated with low-normal serum testosterone levels. These endocrine abnormalities returned to normal after tonsillectomy and adenoidectomy but no reference was made to arterial blood gases either before or after treatment and no

Responses of LH and FSH to injected GnRH and TSH and Prolactin to injected TRH in a man with obstructive sleep apnoea (Pickwickian) syndrome at various stages during weight reduction diet

Day	PaO_2 (kPa)	Serum											
		LH response (U/l)			FSH response (U/l)			TSH response (mU/l)			Prolactin response (mU/l)		
		0'	30'	60'	0'	30'	60'	0'	30'	60'	0'	30'	60'
3	6.4	6.4	23	20	3.0	5.5	6.4	<1.0	<1.0	<1.0	140	300	240
15	7.7	5.8	23	22	7.2	12	12	<1.0	<1.0	<1.0	150	380	250
57	8.8	3.5	14	12	2.8	5.4	6.2	<1.0	<1.0	<1.0	84	360	230
126	9.2	4.5	32	28	5.0	12	13	<1.0	4.1	1.8	60	ND	ND
Normal range		UD-9.0	20-42	20-38	UD-7.0	4-18	4.5-21	UD-8.0	Increment>3.6 30'>60'		60-360	Increment>65% of basal 30'>60'	

Table 34

explanation for the endocrine suppression was offered. This finding of low LH production during sleep supports our earlier postulate (chapter X)[168] that hypoxic dips during REM sleep may suppress LH production. Sleep laboratory studies will be required to confirm this. Growth hormone production during sleep has also been found to be suppressed in this clinical condition[251] offering further evidence of nocturnal pituitary suppression.

Serum testosterone increase with weight reduction in our case was dramatic (figure 23). Sex hormone binding globulin also rose (figure 24) and this would tend to reduce the level of unbound or free testosterone. However the overall effect was an increase in free testosterone index and free testosterone (figure 24, table 33) from subnormal to normal levels and this net increase in unbound testosterone would be expected to result in improved libido and return to normal of sexual function as indeed occurred. In addition to SHBG, thyroid binding globulin also rose with weight reduction and rise in PaO_2 (figure 25, table 33). The increase in hormone binding proteins in this situation appears to be a new finding and the reason for it is not clear. As with free testosterone, free thyroxine also tended to increase with recovery despite a rise in the hormone binding protein.

It is of great interest that the majority of hormones were positively and significantly correlated with PaO_2. Considering the increase in serum testosterone with increase in PaO_2 (figure 23) it will be seen from the graphs that serum testosterone entered the normal range (11-36nmol/l) on the tenth day of dieting at a PaO_2 of around 7.3kPa (55mmHg) which is virtually identical to that expected according to the regression lines for both COAD and pulmonary fibrosis patients (chapters VI & IX, figures 8 & 18). Whereas this may be coincidental it suggests that hypoxia rather than some non-specific effect of illness is responsible for the testosterone

suppression and possibly also for that of the other hormones.

The normal LH response to injected GnRH (table 34) suggests hypothalamic rather than pituitary suppression as a cause of the deficient steroidogenesis and this also occurred in the majority of our cases with hypoxic pulmonary disease. The absent TSH responses to TRH in the presence of normal T_4 is interesting. Serum T_3 and T_4 did tend to increase with recovery (figure 25) associated with return to normal of TSH response to TRH and one may speculate whether T_4 would have become frankly low if hypoxia had persisted in this patient for some months longer. The rise in the adrenal androgen DHAS but not of androstenedione (table 33) did not surprise us as a similar trend was found in patients recovering from acute phase cor pulmonale (chapter VIII, figure 16).

This patient demonstrates all the fascinating features of the Pickwickian syndrome. It is unusual to encounter an individual so well motivated to diet and to witness such dramatic pulmonary function, arterial blood gas and clinical improvement in this condition. By this stage of our protracted hormone researches in hypoxic chest diseases we were reasonably confident of an association between arterial oxygen and serum testosterone levels so it was no surprise when the testosterone results, assayed in one batch at the end of the study, turned out as they did. Pickwickian subjects are rare so it might be some time before we can confirm our findings.

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